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Structure-based discovery of cyclin-dependent protein kinase inhibitors

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CDK: cyclin-dependent kinase
CBF: cyclin box fold
PK: pharmacokinetic

Abstract

The cell fate-determining roles played by members of the cyclin-dependent protein kinase (CDK) family explain why their dysregulation can promote proliferative diseases, and identify them as potential targets for drug discovery in oncology and beyond. After many years of research, the first efficacious CDK inhibitors have now been registered for clinical use in a defined segment of breast cancer. Research is underway to identify inhibitors with appropriate CDK-inhibitory profiles to recapitulate this success in other disease settings. Here we review the structural data that illustrates the interactions and properties that confer upon inhibitors affinity and/or selectivity towards different CDK family members. We conclude that where CDK inhibitors display selectivity, that selectivity derives from exploiting active site sequence peculiarities and/or from the capacity of the target CDK(s) to access conformations compatible with optimizing inhibitor-target interactions.

Summary points

- Type I, “1.5”, II and III inhibitors have been described for CDKs
- Type I inhibitors engage the hinge through a range of hydrogen and/or halogen-bonding motifs
- CDKs have a bulky gatekeeper which can contribute to inhibitor binding or be manipulated to permit selective inhibition/co-factor utilization
- Plastic rearrangements of the glycine lid may play a role in inhibitor selectivity by allowing read out of sequence differences remote from the active site
- A “selectivity surface” adjacent to the ATP-binding site differs in character in different CDK subfamilies, and can be predictably targeted to provide a degree of selectivity
- The C-terminal tail can contribute to inhibitor contacts in transcriptional CDKs
- A subset of CDKs may be targeted by covalent, thiol and amine-reactive inhibitors

Introduction

Originally identified as regulators of the eukaryotic cell cycle, CDKs also regulate transcription and, in certain cell types, differentiation [1-3]. The activities of CDK family members impact several hallmarks of cancer [4]. In specific cellular settings, inappropriately elevated CDK activity, for example that of the cell cycle regulators CDK2, CDK4 and/or CDK6, has been identified as a cancer driver [5-8]. Expression or mutation of the activating cyclin subunit or decreased expression or mutation of an inhibitor (for example members of the INK family that bind specifically to CDK4 and CDK6) are frequently observed cancer-associated alterations (http://cancer.sanger.ac.uk/cosmic). CDKs 7, 8, 9, 11 and 20 regulate the synthesis of mRNA and therefore, by changing patterns of gene transcription, impact cell survival and differentiation [3, 9]. As a reflection of their differing roles in tissue physiology, aberrant activity of cell cycle or transcription regulatory CDKs can initiate or drive tumor progression in a cell-type specific manner, offering the opportunity to target specific cancers with CDK-selective inhibitors in certain patient populations.

CDK active and inactive states

A conserved feature of protein kinase activation is remodeling of an inactive monomeric kinase fold in response to protein association and /or post-translational modification [10, 11]. The structure of monomeric CDK2 revealed how an inactive state derives from misalignment of residues required for productive substrate binding and catalysis [12]. Association with a cognate cyclin and, for most CDK-cyclin pairs, phosphorylation of a conserved threonine residue within the activation loop, are minimal pre-requisites for full activity [1, 13, 14]. However, the catalytically competent structure can be inferred to form only upon binding of ATP and peptide substrates: the conformation of the C-helix of CDK4 in complex with cyclin D resembles that of inactive, monomeric CDK2, suggesting the need for further conformational change in the Michaelis complex to enable phosphotransfer (**Figure 1a, b** [15]).

One challenge for drug development is that 20 members of the CMGC subfamily of the human kinome are sufficiently related to be classified as CDKs [3, 16]. Among these proteins, sequence identity is high within the residues that directly line the CDK active site (**Figure 1c, d**), and their convergence to a conserved structure upon activation has presented challenges for the design of inhibitors that target individual family members. Nevertheless, the available sequence diversity and conformational plasticity of the CDK

fold have together offered opportunities to derive potency and selectivity. However, most inhibitor series exhibit substantial activity for a subset of the family.

The most successful clinical approach to date has involved targeting CDK4 and CDK6 [8, 17, 18]. This strategy exploits structural properties of CDK4 and CDK6 that distinguish them from the rest of the family: CDK4 bound to cyclin D and phosphorylated on the activation loop preserves “inactive” structural features observed in monomeric CDK2, suggesting a mechanism wherein only when both ATP and peptide substrate are engaged is the catalytically competent conformation formed ([19, 20]; **Figure 1b**).

We will review how CDK structural biology has assisted the design of CDK inhibitors, highlighting structural properties that have been exploited to provide selectivity. Accordingly, we will limit our discussion to inhibitor series for which structures bound to the target CDK have been determined.

The CDK ATP binding site

Conformational change is an essential element of protein kinase function. It has been hypothesized that the conformations that have been observed in protein kinase-inhibitor complexes represent snapshots of states that might exist through the catalytic cycle [21]. Inhibitors that capture the kinase target in particular conformational states have been categorized as type I, II, III or IV depending on whether they mimic the interactions of ATP with a catalytically competent kinase active site (DFG-in, type I); occupy the ATP binding site and stabilize a catalytically inactive DFG-out conformation (type II); are non-competitive with ATP and bind to an hydrophobic pocket adjacent to the ATP binding site (type III) or are allosteric (type IV), binding away from the ATP binding site [22].

The first type I CDK inhibitors whose development was informed by structural biology were targeted against CDK2 (**Table S1**, [23]). These structures illustrated how inhibitor binding can (i) satisfy the hydrogen bonding potential of the backbone Glu81 carbonyl and Leu83 amide moieties within the hinge sequence (which anchor the adenine N1 and N6 of ATP respectively), (ii) offer a planar moiety that mimics the adenine ring, (iii) fill the binding pocket to contact residues that do not contact ATP, and (iv) probe the ribose and phosphate binding sites (**Figure 2**).

Dinaciclib (IC_{50} values against CDKs 1, 2, 5 and 9 of 3, 1, 1 and 4 nM respectively [8]) has undergone advanced phase III clinical trials and is currently being considered in combination therapies [24, 25]. The structure of dinaciclib bound to CDK2 illustrates the binding mode of this class of type I pan CDK inhibitor (**Figure 2b**, PDB 4KD1). It also

reveals the challenges of achieving selectivity within the highly-conserved ATP binding site: many of the residues that directly contact ATP are identical among CDKs.
There are variations in the ways that adenine mimetics can bind to the hinge that links the N- and C-terminal lobes: 4-(1,3-Benzothiazol-2-yl)thiophene-2-sulfonamide (compound **4a,** CDK5 IC_{50} 551 nM) bound to CDK5-p25 makes a water-mediated interaction (PDB 4AU8, [26], **Figure 2d**), as does a series of 2, 4, 6-tri-substituted quinazolines that targets CDK2 (CDK2-compound **51**, PDB 2B53, CDK2 IC_{50} 0.6 ± 0.1 uM, [27]). 6-aza-benzothiophene-containing compounds targeting CDK8 (for example compound **22**, IC_{50} CDK8 5.3 nM) form a single hydrogen bond to the hinge residue Ala100 (equivalent to CDK2 Leu83, PDB 5CEI, [28], **Figure 2e**), whereas DRB (5,6-dichlorobenzimidazone-1-b-*D*-ribofuranoside), a CDK9-selective inhibitor (CDK9 IC_{50} 230 nM [29]) exploits halogen bonds (PDBs 3MY1, 4EC8, [29, 30], **Figure 2f**). The potential to make a third hydrogen bond to the backbone carbonyl equivalent of CDK2 Leu83 may be exploited to anchor and/or orientate the purine mimetic to optimize vectors to exploit sites beyond the adenine binding site (e.g. PDB entries 3DDQ and 1H1S, [31, 32], **Figure 2c**). Notably, although inhibitors make direct interactions with backbone moieties, sequence differences within the hinge appear to impact inhibitor potency and selectivity, presumably through effects on the relative orientations of the N- and C-terminal lobes and domain flexibility [33-35]. Such effects are difficult to rationalize, but are supported by results derived from CDK2 mutants in which the hinge sequence has been changed to that of CDK4 or CDK6 [36, 37].

The gatekeeper pocket

The CDK active site cleft is larger than is required for cofactor binding, and the additional space within the cleft has been widely exploited. At the back of the cleft, CDKs have a large gatekeeper residue (phenylalanine in all members except CDK10, 11A and 11B where it is a methionine) that can make multiple interactions. For example, edge-to-face aromatic-aromatic interactions are exploited in (i) a series of 4-anilinoquinazolines targeting CDK2 (PDB 1DI8, [38]), (ii) 7-azabenzimidazoles (*e.g.* CDK6-compound **3**, PDB entry 4EZ5, IC_{50}s vs CDK4/6 12 ± 2/300 ± 100 nM, >15 uM vs CDK1/6.2 ± 0.4 uM CDK2, [35], **Figure 3a**), and 4-(pyrazol-4-yl)-pyrimidines targeting CDK4/6 (*e.g.* CDK6-compound **37** PDB 3NUP; IC_{50} CDK4-cyclin D1 12 ± 1 nM; [39]), and (iii) pyrido[4′,3′:4,5]pyrrolo[2,3-d]pyrimidine derivatives characterized as dual FLT3/CDK4 inhibitors (*e.g.* CDK6-compound **1**, PDB 4TTH, FLT3 IC_{50} 14 nM/CDK4-cyclin D1 IC_{50}, 2 nM, [40]).

Favorable halogen-aromatic interactions are made in a quinazoline series that targets CDK2 (PDB 2B53, [27]), in the 4-(pyrazol-4-yl)-pyrimidines series mentioned above that targets CDK4/CDK6 (CDK6-compound **50** PDB 3NUX, CDK4-cyclin D1 IC_{50} 11 nM; [39]), in CCT251545, that

targets CDK8, (PDB entry 5BNJ, [41]) and CCT251921, that targets CDK8 (IC_{50} 2.3 ± 0.8 nM) and CDK19 (IC_{50} 2.6 ± 0.4 nM, PDB 5HBJ [42], **Figure 3b**).

The sulfur atom of the thiadiazole scaffold in a CDK8-compound **6** structure (PDB 5ICP, CDK8 IC_{50} 3.8 ± 1.9 nM [43], **Figure 3c**) has also been reported to interact with the phenylalanine sidechain. The thio-methylene moiety in a series of 2-amino-5-thioalkyl-substituted thiazoles bound to CDK2 occupies a hydrophobic pocket to which Phe80 contributes (PDB 4LYN, [44].

A preference for type I over type II inhibitors derives in part from the bulky character of the gatekeeper residue in CDKs. Mutation of this residue to a smaller amino acid allows access to the back pocket and has been used in conjunction with modified ATP or inhibitors to respectively identify CDK substrates and as a probe for CDK function [45, 46]. Many inhibitor series build from this region to make either direct or water-mediated interactions with the conserved lysine-glutamate pair (Lys33 and Glu51 in CDK2) that coordinates the ATP alpha-phosphate group. Filling this back part of the cleft with small, branched aromatic or halogen-rich moieties is common feature of a number of inhibitor series. Notably larger moieties can flip the inhibitor binding mode offering alternative options for inhibitor design from a conserved scaffold.

The DFG motif and back pocket remodeling

The character of this region of the active site depends crucially on the DFG conformation [22, 47]. The first observation of a DFG out cyclin-bound CDK structure was that of CDK8 bound to cyclin C and sorafenib (**Figure 4a**, PDB 3RGF [48]), a type II inhibitor of other protein kinases [49]. Starting from sorafenib, a series of CDK8 inhibitors stabilizing the DFG-out (DMG-out in CDK8) conformation were developed (*e.g.* CDK8-cyclin C-compound **20**, CDK8 IC_{50} 17.4 nM, PDB 5HVY, [50]). CDK8 demonstrates flexibility in this part of the structure as apo-CDK8-cyclin C has a DMG-in structure (PDB 4F7S, [51]). A number of CDK8-cyclin C-type I inhibitor co-complexes have been reported, including CDK8-cyclin C bound to cortistatin A (PDB 4CRL, [52], **Figure 4b**) and a series of azabenzothiophene derivatives (PDB 5CEI, [28]. Reflecting their close phylogenetic

relationship, a number of type I inhibitors have been developed that are selective for CDK8 and CDK19. These include CCT251545 (CDK8-K_d 2 nM, PDB 5BNJ, [41]), 2,8-disubstituted-1,6-naphthyridine- and 4,6-disubstituted-isoquinoline-based ligands [53] and a series of compounds based on a 3-methyl-1H-pyrazolo[3,4-b]-pyridine scaffold (*e.g.* MSC2530818, CDK8 IC_{50} 2.6 ± 0.1 nM, PDB 5IDN, [43]).

Prolonging the engagement of an inhibitor with its target can lead to improved pharmacokinetic (PK) properties and greater efficacy [54, 55], and has been reported as a characteristic of type II protein kinase inhibitors that target tyrosine kinases [47]. However, within a set of inhibitors that elaborated a pyrazole urea based scaffold (PDBs 4F6S, 4F7J, 4F70, 4F6U, 4F7N, 4F7L and 4F6W, [51]) residency time did not track with DMG conformation, but rather was hypothesized to derive from interactions with the hinge and the "selectivity surface" on the kinase C-terminal lobe. However, some PK optimization of CDK inhibitors has been rationalized by structural insights. Roniciclib (BAY 1000394) is a type I pan CDK inhibitor which exhibits kinetic selectivity for CDK2 and CDK9 [56]. CDK2 showed a DFG loop adaptation as a response to the presence of a 5-(trifluoromethyl) substituent, but not of a hydrogen or bromine atom substitution (Compare PDBs 5IEV and 5IEX). A distinguishing feature of the trifluoromethyl-substituted inhibitor-bound CDK2 structure was the network of water molecules between the inhibitor moiety, the DFG motif and the gatekeeper, Phe80. The DFG conformation was distinct from the DFG-out conformation characteristic of other protein kinases, but had been previously observed in the CDK2-R547 structure (CDK2 K_i 1 nM, PDB 2FVD, [57]).

The ATP ribose phosphate binding pocket

There are fewer reports of rational SAR where interactions offered by the ribose-phosphate binding pocket have been targeted. This part of the active site is composed of a number of flexible loop regions (**Figure 5a**) making rational design difficult: molecular dynamics simulations conducted on CDKs and CDK-cyclin complexes have illustrated that the glycine-rich lid is highly dynamic in nature [58]. The determination of the structure of CDK5 bound to p25 (PDB 1H4L, [59]) revealed that its active site is very similar to that of CDK2. However, there is local restructuring upon both (*R*)-roscovitine (PDB 1UNL, [60]) and compound **1.0** binding (PDB 3O0G, [61]) to yield an unusual glycine-rich loop conformation, that presumably reflects the CDK5-specific aspects of the sequence in this region (**Figure 5b**). Similarly, binding of an aminopurine derivative bearing a bulky biphenyl substituent at the 6-position has been observed to stabilize a glycine-rich loop

conformation that is preferred in CDK2 (PDB 5LQE) and that has not been observed in CDK1 (PDB 5LQF) [62]. Though difficult to rationalize, the *circa* 2000-fold selectivity of this biphenyl derivative for CDK2 over CDK1 must derive from differences in conformational preferences supported by the CDK1 or CDK2 folds.

Within a series of 4-(thiazol-5-yl)-2- (phenylamino)pyrimidine-5-carbonitriles, a comparison of inhibitor binding to CDK2 and CDK9 (E.g. compare binding of compound **12u**, CDK2 and CDK9 K_is of 568 nM and 7 nM and PDBs 4BCP and 4BCG respectively [63]) illustrates how, despite a broadly conserved binding pose, subdomain movements and local conformational flexibility around the CDK9 active site can drive compound selectivity (**Figure 5c**, [63, 64]). Comparing the structures of CDK9-cyclin T bound to a more diverse inhibitor set reveals that significant movements of the glycine-rich loop (and also of the beta3-alphaC loop) frequently accompany potent CDK9 inhibitor binding ([29, 65, 66], **Figure 5d**).

The selectivity surface

To discriminate more effectively between CDKs, the sequence differences immediately outside the active site on the surface of the C-terminal lobe can be probed by extending out from the purine binding site. This surface is quite different in character between CDK1/2 (PDBs 4YC3/1JST), CDK4/6 (PDBs 2W96/1JOW) and CDK8/9 (PDBs 3RGF/3BLQ), (as shown in **Figure 6**: equivalent residues in other CDKs can be inferred by reference to **Figure 1c**).

Various CDK4/6-selective inhibitor series exploit the surface, for example offering substituted piperazine moieties capable of favorable polar interactions with the hydroxyl side chain of CDK4 Thr102 or CDK6 Thr107, but being repulsed by the charge on CDK2 Lys89 [40]. Palbociclib (PDB 2EUF, [34], **Figure 6a**) and ribociclib (PDB 5L2T, [67], **Figure 6b**) bound to monomeric CDK6 nicely illustrate how this surface can be exploited. Together with neighboring amino acids, the peptide chain around Lys89 shapes a groove that can be exploited to derive CDK1/2 selectivity. As examples, the 4'-sulfamoylanilino group present in NU6102 sits within this pocket and makes hydrogen bonds to the sidechain carboxylate and peptidic nitrogen of Asp84 (PDB entry 1H1S, [32], **Figure 6c**). CDK2 Lys89 has also been targeted by a covalent strategy [68]. The flexibility of the CDK9 sequence following the hinge accommodates the bulky, substituted aniline moieties that drives compound selectivity in a series of substituted 4-(thiazol-5-yl)-2-(phenylamino)pyrimidine-5-carbonitriles (PDB entries 4BCF, 4BCH, 4BCI, 4BCJ, 4BCM,

4BCN, 4BCK, 4BCO, 4BCQ, [63, 64], **Figure 6d**). Coupled to groups that probe sequence differences, the most successful compounds have identified a vector from the purine mimetic such that the conformation of the bound inhibitor is relatively strain-free and entropically favored because of pre-organization of the free ligand.

CDK4/6 lend themselves to selective inhibition and show clear disease linkage

CDK4 and CDK6 are the best validated CDK targets in the largest number of clinical settings [17]. Although no structures have been reported for such inhibitors bound to CDK4/6-cyclin D complexes, drug discovery programs have developed CDK4/6-selective inhibitors of which two, ribociclib [69] and palbociclib [33] are approved for the treatment of hormone receptor positive and human epidermal growth factor receptor-2 negative (HR+/HER2−) breast cancer. This success has been driven in part by the ability to identify patients where enhanced CDK4 or CDK6 activity is a driver of cancer progression (http://cancer.sanger.ac.uk/cosmic). It can also be hypothesized that the unusual plasticity of CDK4, and potentially also that of CDK6, allows the development of potent and selective inhibitors despite the high degree of sequence conservation within CDK active sites. However, it is worth noting that the responses of CDK4 and CDK6 to cognate cyclin binding may differ. CDK4 does not adopt a fully active conformation upon cyclin D and activation segment phosphorylation (PDB 2W96, [20], whereas viral cyclin binding drives CDK6 to adopt an active conformation in which the activation segment is not phosphorylated but would be predicted to accommodate a peptide substrate (PDB 1JOW, [70]).

In the absence of structures for inhibitors bound to active CDK4/6-cyclin D, it is difficult to rationalize inhibitor properties. However, structures were used to guide optimization of a series of 4-(pyrazol-4-yl)-pyrimidines as CDK4/6 inhibitors using monomeric CDK6 as the template (E.g. CDK6-compound **50,** CDK4-cyclin D1 IC_{50} 11 nM, [39]). Structures of monomeric CDK6 bound to several clinical candidates have now been determined (PDB entries (5L2S, abemaciclib; 5L2W, dinaciclib; 5L2I, palbociclib; 5L2T, ribociclib, [67]). More detailed rationalization of their inhibitory properties awaits their structure determination bound to a CDK4/6-cyclin D complex.

The C-terminal tail

The transcriptional CDKs are characterized by extended C-terminal sequences beyond the conserved kinase domain. Though few inhibitor co-complex structures have been

determined for this transcriptional CDK sub-class, emerging data shows how the C-terminal tail can impact the character of the ATP binding site. The CDK9 tail shapes the catalytic cleft and its conformational cycle results in an ordered binding of substrates and release of products (PDB 4EC8, [30]). It is exploited by the CDK9 inhibitor 5,6-dichlorobenzimidazole 1-b-D-ribofuranoside (DRB) that is a more potent inhibitor of full-length CDK9 than C-terminally truncated variants. DRB binding locks the CDK9 N- and C-terminal lobes in an orientation that favors the ordering of the C-terminal sequence (**Figure 7a**). Similar trapping of AMP-PNP in a closed state assisted by residues located within the C-terminal extension is observed in the structure of a CDK12-cyclin K-AMPPNP complex (PDBs 4NST, [71]; and 4CXA, [72]). Although there are no deposited structures for CDK13-cyclin K bound to ATP-competitive inhibitors, the CDK13 structure reveals a similar C-terminal helix that extends into the active site where it interacts with ATP (PDB 5EFQ, [73]). The CDK8 C-terminal tail also reaches up into the active site and, in the presence of the ATP-competitive inhibitor CCT251545 (a 3,4,5-trisubstituted pyridine) makes a favorable cation-pi interaction between the phenyl ring of the inhibitor and the guanidine moiety of Arg356 (PDB 5BNJ,[41], **Figure 7b**). Indeed, representatives from diverse chemotypes have now been crystallized with CDK8-cyclin C and, irrespective of the orientation of the DMG sequence, significant interactions are made with the C-terminal tail sequence.

CDK7, CDK12 and CDK13 contain cysteine residues within their extended C-terminal sequences. These residues offer the possibility of targeting by covalent inhibitors and, as they are outside the kinase core fold, achieving greater selectivity. THZ1 is a potent and selective chemical probe targeting CDK7 [74] and covalently interacts with Cys312, a residue that is not built in the CDK7 crystal structure (which terminates at Asn311, PDB 1UA2, [75]). CDK12 and CDK13 have a cysteine residue within 4 residues of CDK7 Cys312 and THZ1 does indeed inhibit CDK12 and CDK13 at higher concentrations [74]. The structure of the THZ531 bound to CDK12-cyclin K reveals the re-arrangements within the CDK12 C-terminal lobe that re-orients the cysteine sidechain (Cys1039) to permit the covalent interaction to form (PDB 5ACB, [76], **Figure 7c**). Indeed THZ (and derivatives) is proving to be a useful tool compound to delineate transcriptional CDK activity in defined cellular settings [76].

Targeting the monomeric enzyme

Unconstrained by catalytic requirements, CDKs are more diverse in structure when monomeric than cyclin-bound and, correspondingly, show less well conserved patterns of inhibitor binding [77]. Such observations have prompted studies to identify type II and type III inhibitors that can stabilize monomeric CDKs in conformations that are incompatible with catalytic activity and/or cyclin binding.

Most progress towards this aim has been made with CDK2. Although it was originally thought that CDK2 would not be amenable to adopting a DFG-out structure, judicious screening identified an aminopyrimidine-phenyl urea inhibitor (K03861) that stabilized such a conformation [78]. This conformation proved to be competitive with cyclin binding and to have a slow k_{off}, *i.e.* to have characteristics consistent with a type III inhibitor.

Moving away from the active site, high concentrations of 8-anilino-1-naphthalene sulfonate (ANS) can drive formation of a large pocket that accommodates two adjacent ANS molecules, extending from the DFG region to above the C-helix [79]. The shift in the C-helix position was predicted to be incompatible with cyclin binding, a hypothesis confirmed by competitive binding studies (**Figure 8a**).

In another approach, a high throughput screen has identified compounds that bound to inactive unphosphorylated monomeric CDK2 rather than phosphorylated CDK2-cyclin A. A type I.5 quinolone-based inhibitor (DFG-in, occupying the ATP-binding site and adjacent non-canonical pockets, compound **14**) was subsequently developed with a K_d of 5 nM, determined using a temperature-dependent circular dichroism assay [80]. The binding mode of this series is illustrated by a CDK2-compound **2** complex structure (K_d 300 nM). In this structure, the hydroxyphenyl moiety of the inhibitor binds to the hinge, the DFG motif is in the “in” conformation, and a quinolone 3-chlorophenyl group sits in a hydrophobic pocket under the C-helix. Occupation of this pocket translates and rotates the C-helix into a position incompatible with cyclin association (PDB 4NJ3, **Figure 8b**). Inhibitors that block cyclin binding might be expected to exert different cellular effects from those that sequester cyclins into an inactive complex. Whether such differences in activity translate into novel therapeutic possibilities awaits the identification of cell active type III CDK inhibitors.

Conclusions

As surveyed above, a range of structural properties have reportedly been exploited to maximise selective inhibition of CDK family members. These properties can be grouped

into categories as follows: i) relating to unique or less common sequence features (including residues that may be exploited for irreversible inhibition, residues that flank the cofactor binding site, gatekeeper residues, and residues of the C-terminal tail of transcriptional CDKs), ii) relating to uncommon conformations that can be accessed by loops and residues that line the active site of CDK family members (including the P-loop, the DFG motif, and the C-terminal tail of transcriptional CDKs), and iii) relating to the more diverse structural properties and increased plasticity of the cyclin-free forms of the enzymes. As applies with any categorization, the groupings identified here are blurred in places: sequence differences within the CDK hinge can apparently be read out by inhibitors that don't contact the sidechains directly, a source of selectivity that could be categorized under heading (i) or heading (ii). In practice, however, selective inhibition is likely to derive from a composite of effects, and to be achieved through painstaking exploration of the static and plastic qualities of each CDK as it responds to the binding of different inhibitor series.

For more general strategies that have not been fully explored to date, maybe the most interesting are those that relate to either allosteric modulation, involving binding to sites on CDK-cyclin complexes remote from the ATP binding site, and/or exploiting the less well conserved structures of monomeric states of CDKs.

With palbociclib and ribociclib now approved for use in therapy, the tractability of this target sub-family is now firmly established, paving the way for further clinical development targeting other CDKs. Results suggest that development of all kinase inhibitor types (I through IV) may be possible for the CDK sub-family, and have identified static and plastic properties of CDKs and their inhibitors which can provide a sufficient degree of selectivity for use in oncology and, potentially other clinical settings.

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Declarations of interest

The authors declare that there are no competing interests associated with the manuscript. Some work in the authors' laboratories is funded by Astex Pharmaceuticals.

Author contribution statement

All authors contributed to the review of the literature and PDB, and to the writing of this article.

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Figure legends

Figure 1. CDK activation

(a) Cyclin binding and phosphorylation activate CDKs. A notable exception is CDK8-cyclin C where the residue phosphorylated within the activation segment in most CDKs is replaced by an aspartate (CDK8 Asp191). Monomeric CDK2 (light blue, PDB 1HCK) is superposed on phosphorylated CDK2-cyclin A (CDK2: dark blue ribbon, cyclin A: semi-transparent surface, PDB 1JST). The CDK2 activation segment is highlighted in green. (b) Phosphorylated CDK4 bound to cyclin D1 (PDB 2W96) resembles monomeric CDK2 (light blue ribbon, PDB 1HCK). CDK4 and cyclin D1 are represented by an orange ribbon and a semi-transparent surface respectively, with the CDK4 activation segment highlighted in brown. (c) Sequence alignment over the CDK active site. “Zappo” color coding is used to distinguish physicochemical properties [81]. (d) Stereo view of key CDK active site residues colored by conservation (green, conserved; red, non-conserved, [82]).

Figure 2. CDK2 ATP-competitive inhibitors explore the active site

(a) The binding of CDK2 to ATP (PDB 1HCK) is mimicked by inhibitors: (b) CDK2-dinaciclib (PDB 4KD1), (c) CDK2-cyclin A-NU6102 (PDB 1H1S). Within the CDK family, alternative modes of CDK hinge-inhibitor interaction have been observed. (d) CDK5-**4a**, (PDB 4AU8), (e) CDK8-**22**, (PDB 5CEI) and (f) CDK9-DRB (PDB 3MY1). The CDK5, CDK8 and CDK9 folds are colored red, dark green and lilac respectively throughout.

Figure 3. The gatekeeper pocket

CDK inhibitors that bind through hinge motif make a number of interactions with the conserved phenylalanine gatekeeper residue. (a) CDK6-compound **3** (PDB 4EZ5, aromatic-aromatic) (b) CDK8- CCT251921 (PDB 5HBJ, aromatic-halogen) (c) CDK8-compound **6** (PDB 5ICP, aromatic-sulfur). The CDK6 fold is colored cyan. Dotted lines, which elsewhere are used to indicate hydrogen bonds, are used in this panel to indicate contacts between the inhibitors and the gatekeeper residue.

Figure 4. The DFG motif and back pocket remodeling

A comparison of CDK8-cyclin C bound to type II and type I inhibitors (a) CDK8-cyclin C in complex with the type II inhibitor sorafenib (PDB 3RGF). (b) CDK8-cyclin C bound to cortistatin A (PDB 4CRL). Comparing the figures illustrates how sorafenib binding is

incompatible with the DMG-in conformation. (c) DFG-out CDK2 in complex with the type II inhibitor K03861 (PDB 5A14). (d) A comparison of CDK2-cyclin A bound to roscovitine in a DFG-in conformation (ice blue, PDB 3DDQ) again illustrates how a type II inhibitor binding is incompatible with a CDK2 DFG-in conformation.

Figure 5. The ATP ribose phosphate binding pocket

(a) An overlay of CDK structures illustrates the dynamic nature of the glycine-rich loop. CDKs are colored as previously. CDKs 4, 7 and 12 are colored orange, magenta and white respectively. (b) The CDK5 glycine-rich loop is restructured upon binding (R)-roscovitine (PDB 1UNL, crimson). The structure of CDK5-(R)-roscovitine is overlaid with CDK2-(R)-roscovitine (PDB 3DDQ, light blue) and CDK2-cyclinA (PDB entry 1FIN, glycine-loop colored green). (c) Comparison of inhibitor **12u** binding to CDK2 (PDB 4BCP, CDK2 light blue **12u** yellow) and CDK9 (PDB 4BCG, CDK9 lilac and **12u** green) illustrates local conformational flexibility around the CDK9 active site can drive compound selectivity. (d) Comparison of CDK9-cyclin T bound to a more diverse inhibitor set reveals significant movements of the glycine-rich loop and also of the beta3-alphaC loop (PDBs 3BLQ, 3BLR, 3LQ5, 3MY1, 3TN8, 4BCG).

Figure 6. CDK-selective inhibitors exploit sequence differences on the surface of the CDK C-terminal lobe

(a) Monomeric CDK6 bound to clinical candidate palbociclib (PDB 5L2I), (b) CDK6 bound to ribociclib (PDB 5L2T). (c) CDK2-cyclin A bound to NU6102 (PDB 1H1S). The structures illustrate selectivity between CDK2 and CDK6 through interactions of Lys89 and Thr107 respectively. (d) CDK9 has a glycine residue (Gly112) at the equivalent position, illustrated in the structure of CDK9-cyclin T bound to compound **4** (PDB 4BCH).

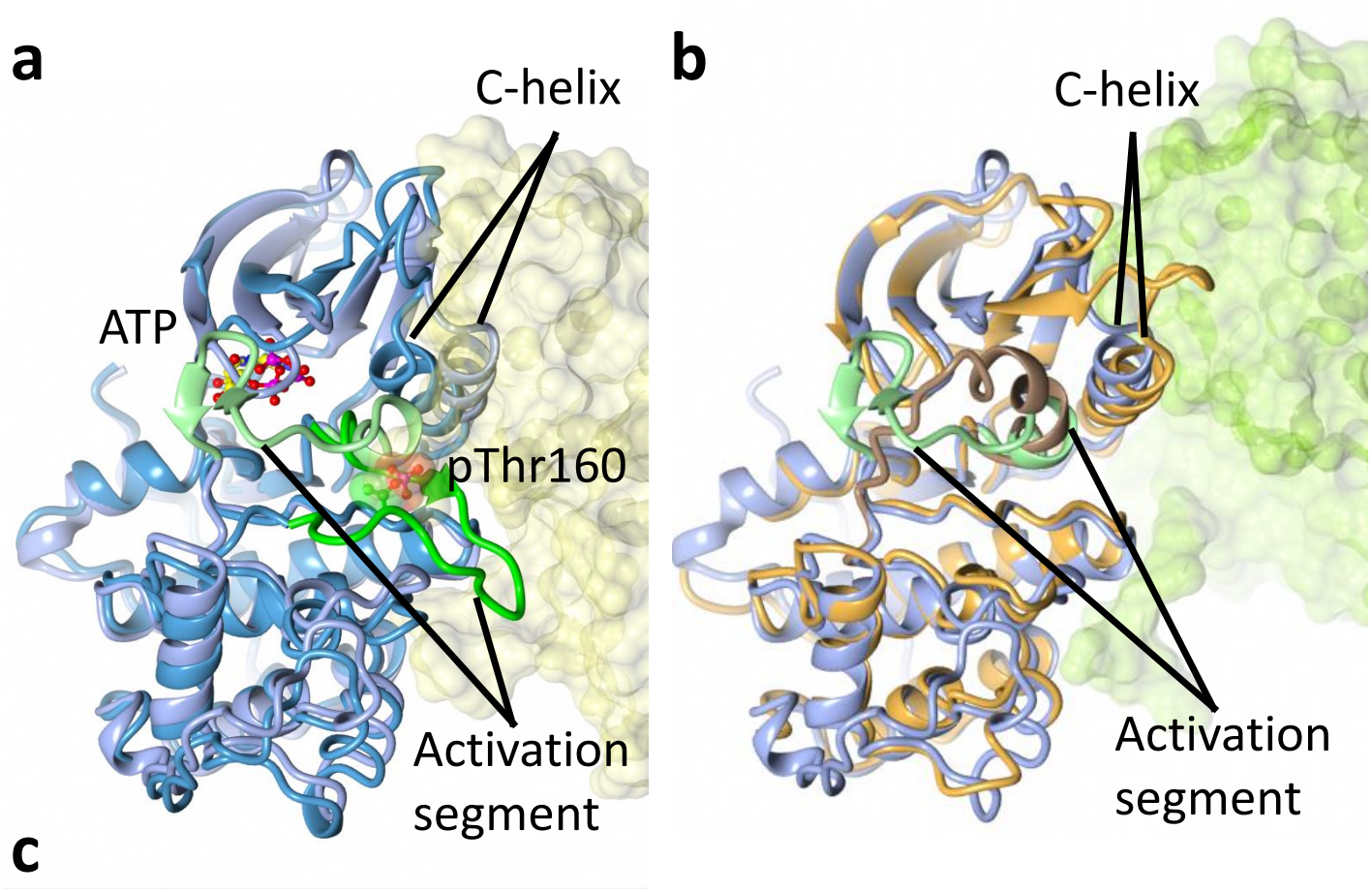
Figure 7. The impact of the C-terminal tail on the catalytic cleft in the transcriptional CDKs.

The transcriptional CDKs are characterized by extended C-terminal sequences beyond the conserved kinase domain, emerging data shows how the C-terminal tail can impact the character of the ATP binding site. (a) CDK9 structure bound to DRB (PDB 3MYC) overlaid with full-length CDK9 (PDB 4EC8). (b) The CDK8 tail also reaches up into the active site as illustrated by the structure of the CDK8-CCT251545 complex. There is a favorable cation-pi interaction between the phenyl ring of the inhibitor and the guanidine moiety of

Arg356 (PDB entry 5BNJ). (c) Similar trapping of the inhibitor THZ531 through the formation of an irreversible bond with Cys1039 located within the CDK12 C-terminal extension, as observed in the structure of a CDK12-cyclin K-THZ531 complex (PDB 5ACB).

Figure 8. Targeting the monomeric enzyme

(a) ANS bound to an allosteric site adjacent to the ATP site, the structural rearrangement creates a large pocket that accommodated two ANS molecules. The shift in the C-helix position was predicted to be incompatible with cyclin binding (PDB entry 3PXQ). (b) Structure of CDK2 bound to type I ½ quinolone-based inhibitor (compound **14**) in which a phenol hydroxyl binds to the hinge, the DFG motif is in the “in” conformation and the quinolone 3-chlorophenyl group sits in a hydrophobic pocket under the C-helix that displaces it out by a translation and rotation to a position incompatible with cyclin association (PDB entry 4NJ3).



c

Residues numbers based on CDK2												
	10	18	33	51	85	86	88	89	131	132	134	145
CDK1	I	V	K	E	M	D	K	K	Q	N	L	D
CDK2	I	V	K	E	Q	D	K	K	Q	N	L	D
CDK4	I	V	K	E	Q	D	R	T	E	N	L	D
CDK6	I	V	K	E	Q	D	T	T	Q	N	L	D
CDK8	V	V	K	E	H	D	W	H	A	N	L	D
CDK9	I	V	K	E	H	D	A	G	A	N	L	D
CDK12	I	V	K	E	H	D	M	G	S	N	L	D

d

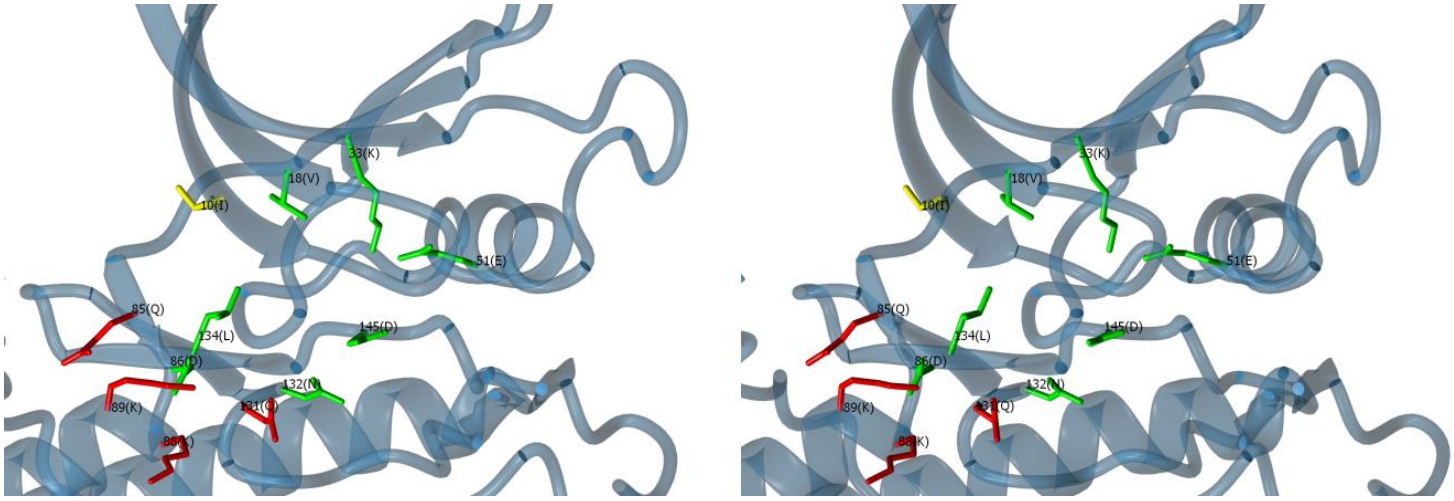


Figure. 1

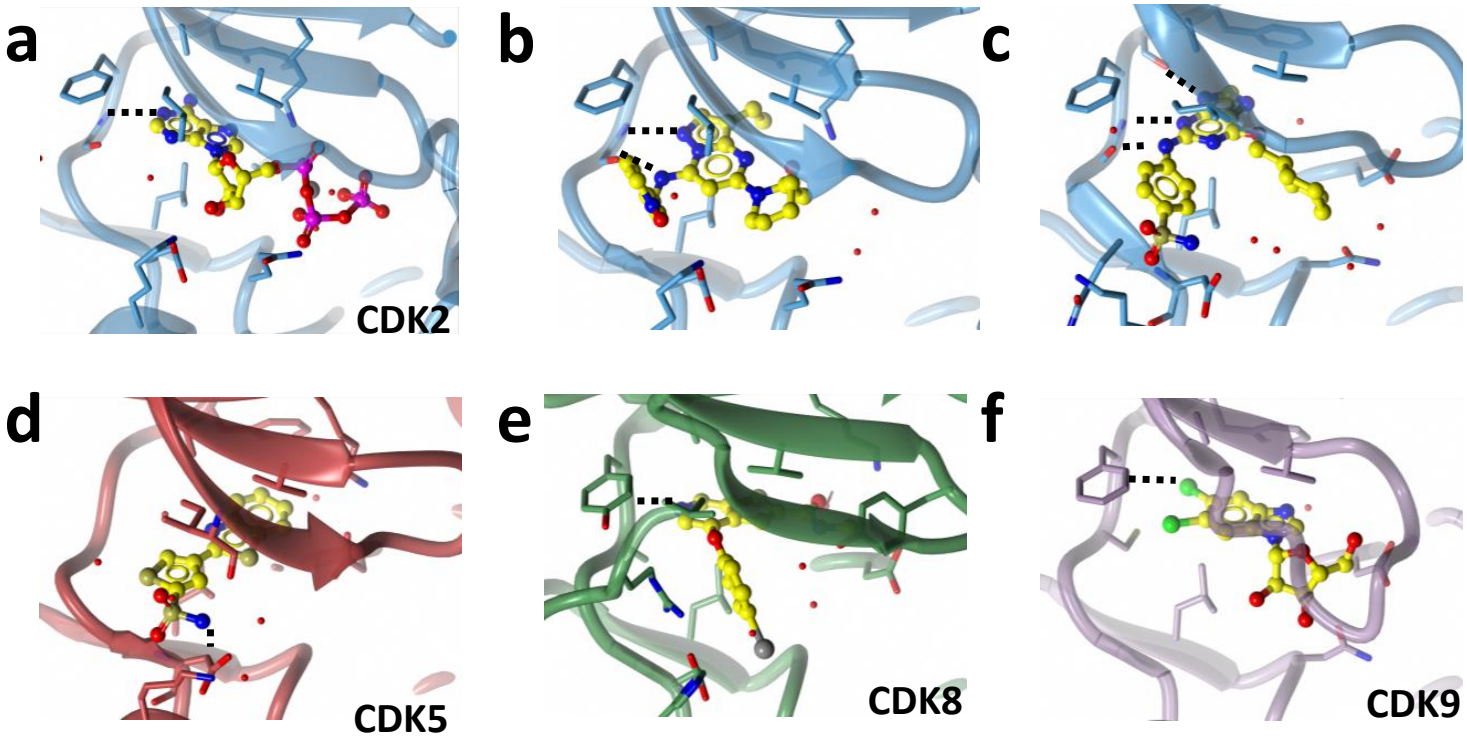


Figure. 2

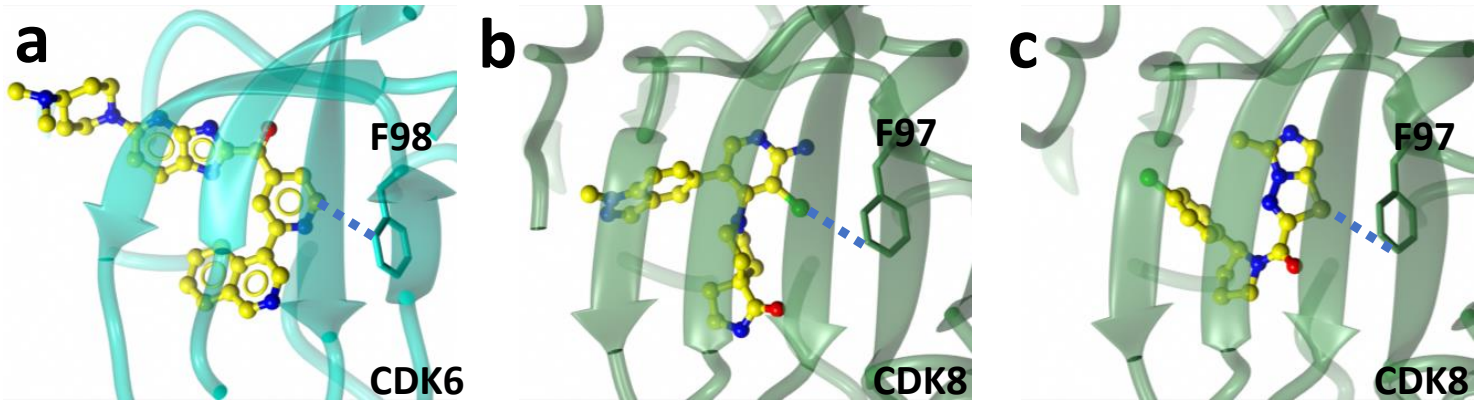


Figure. 3

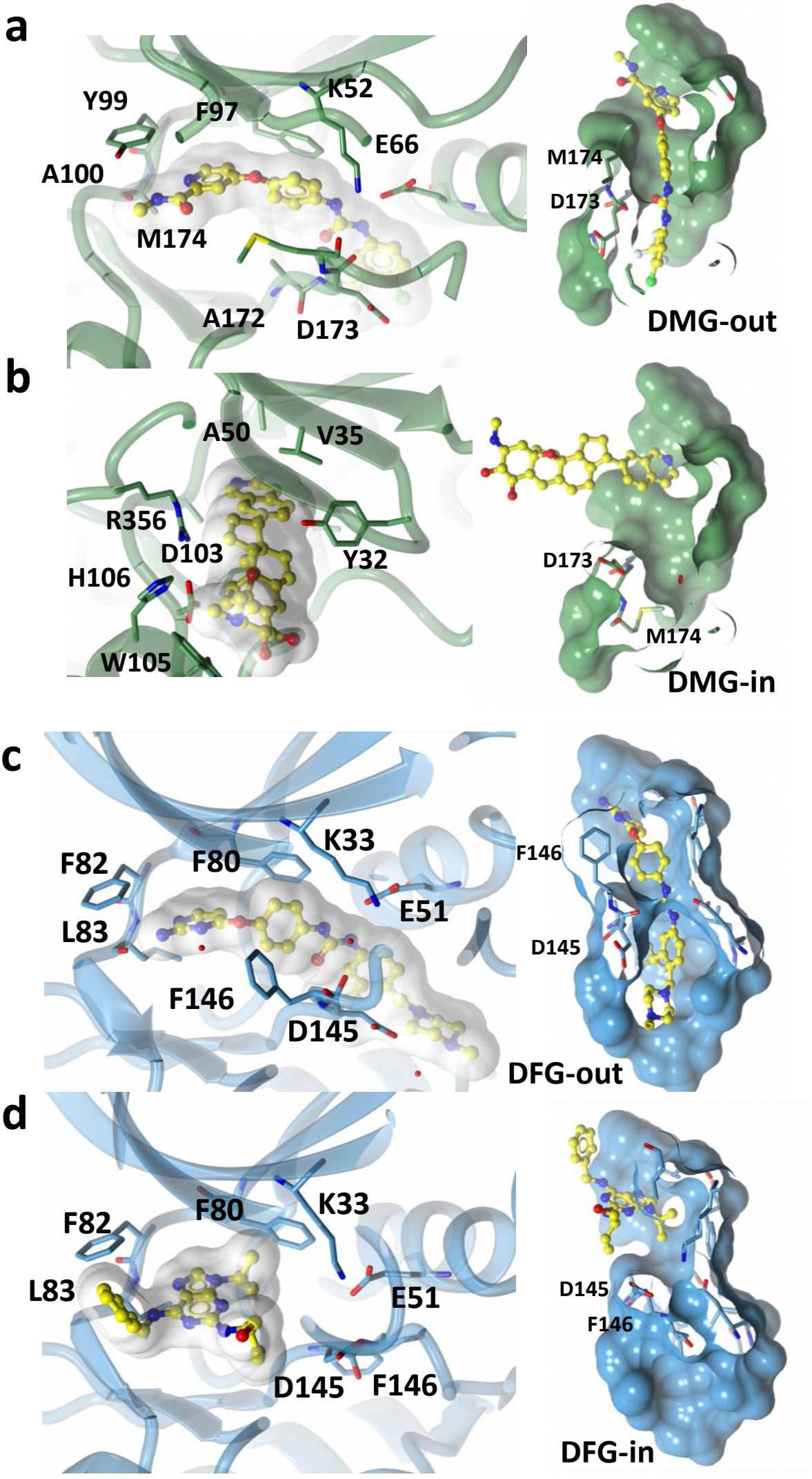

a
Y99
F97
K52
E66
A100
M174
A172
D173
M174
D173
DMG-out
b
A50
V35
R356
D103
Y32
H106
W105
D173
M174
DMG-in
c
K33
F82
F80
E51
L83
F146
D145
F146
D145
DFG-out
d
F80
K33
F82
L83
E51
D145
F146
D145
F146
DFG-in

Figure. 4

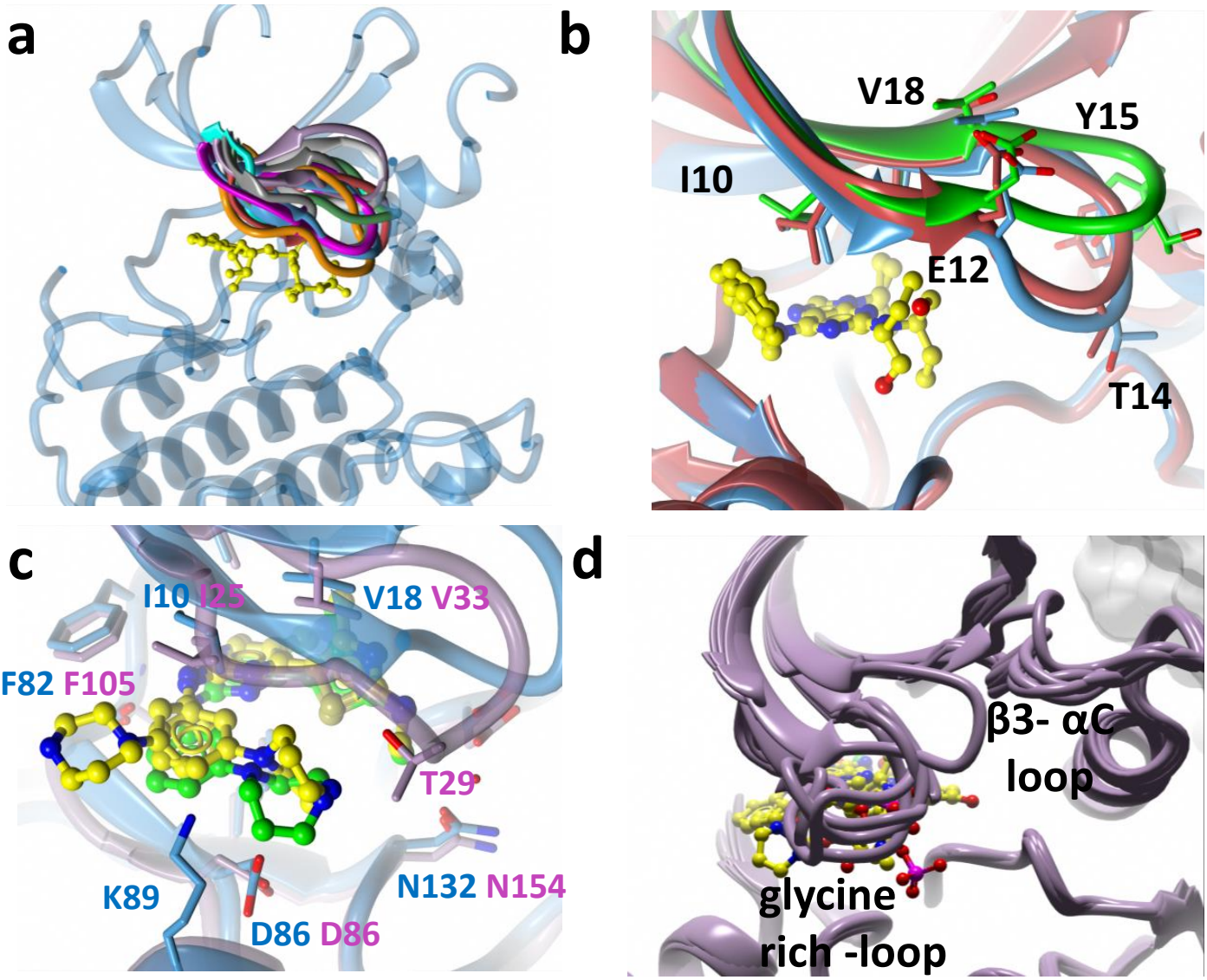

a
b
V18
Y15
I10
E12
T14
c
I10 I25
V18 V33
F82 F105
T29
K89
N132 N154
D86 D86
d
β3- αC
loop
glycine
rich -loop

Figure. 5

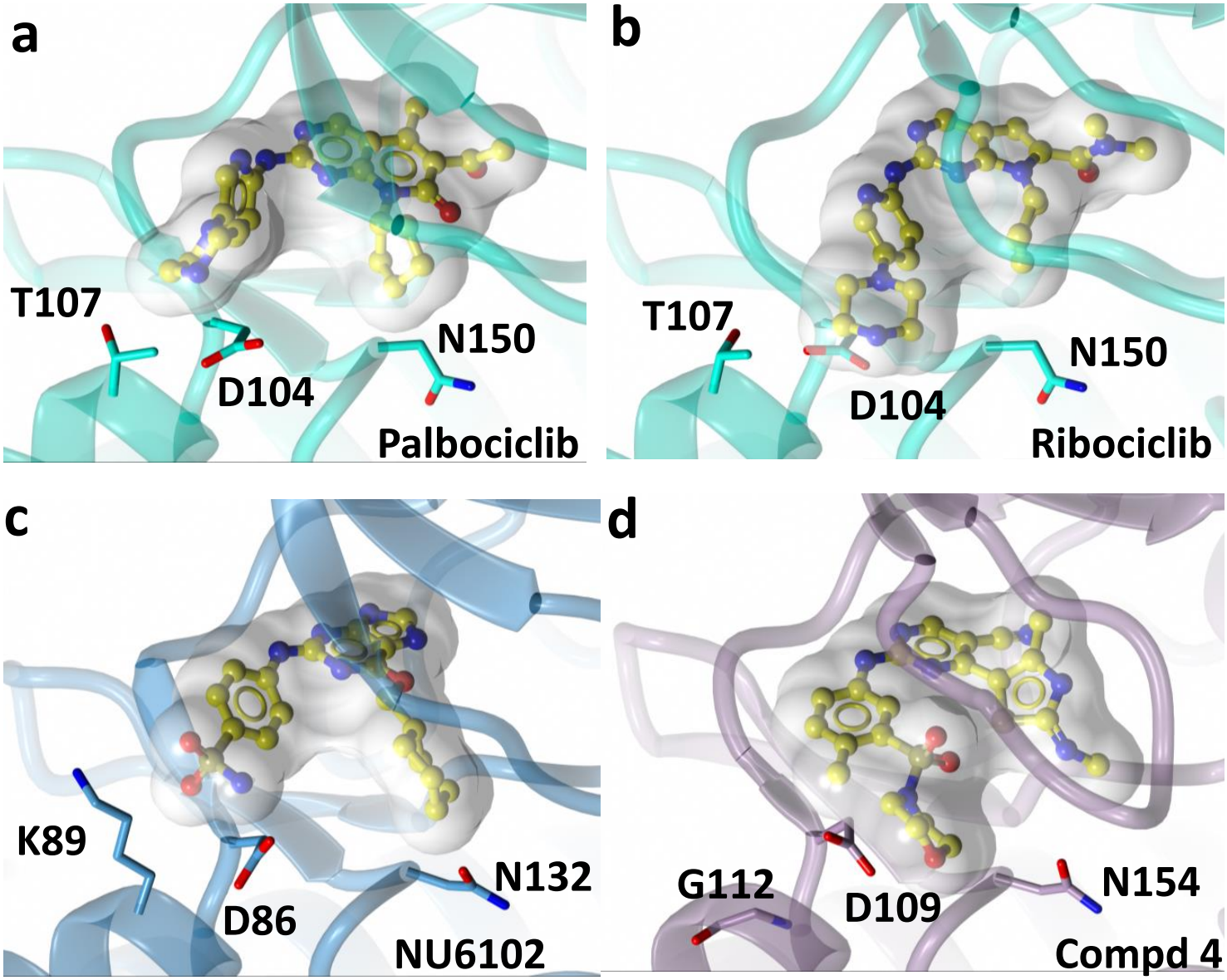

a
T107
D104
N150
Palbociclib
b
T107
D104
N150
Ribociclib
c
K89
D86
N132
NU6102
d
G112
D109
N154
Compd 4

Figure. 6

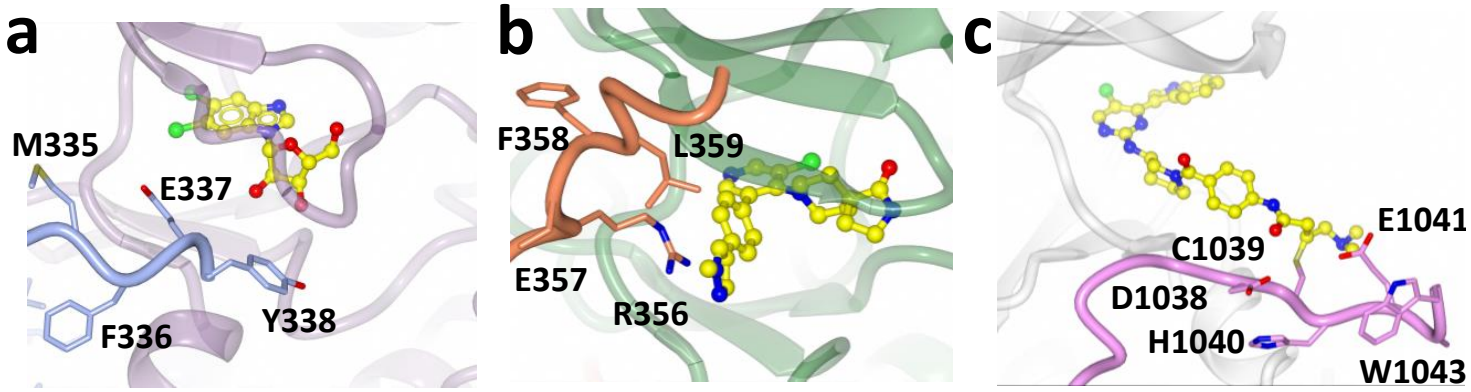

a
M335
E337
F336
Y338
b
F358
L359
E357
R356
c
E1041
C1039
D1038
H1040
W1043

Figure. 7

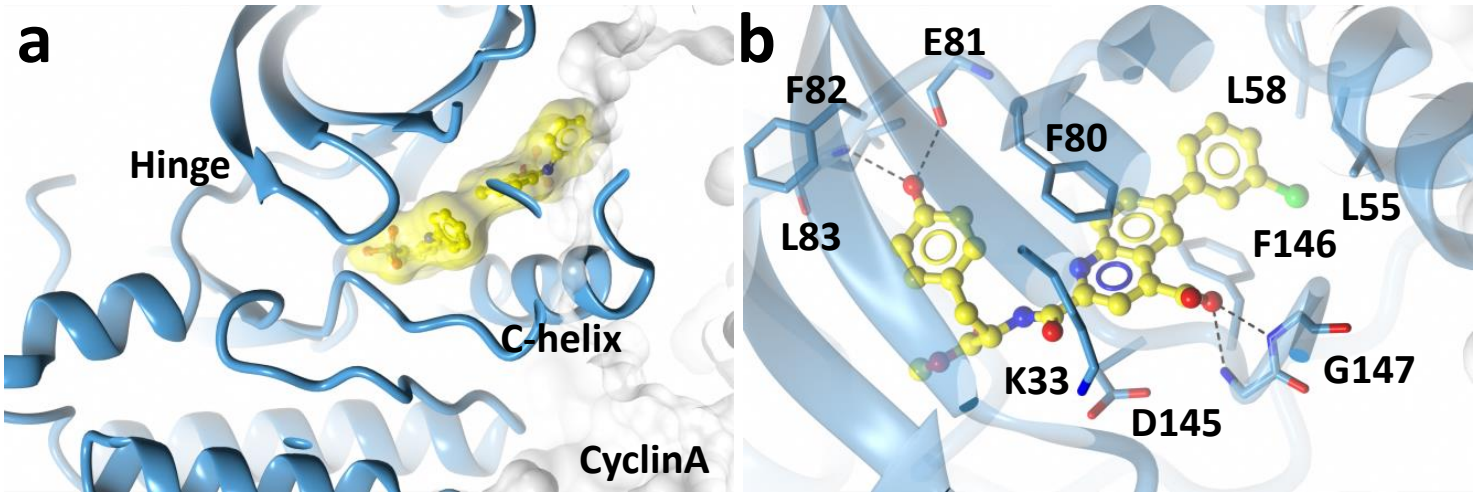

a
Hinge
C-helix
CyclinA
b
E81
F82
L58
F80
L55
L83
F146
K33
G147
D145

Figure. 8

PDB ID	PubMed ID	Structure title	Deposition date	Publication year
CDK1				
4Y72	25864384	Human CDK1-cyclin B1-CKS2 With Inhibitor	2015-02-13	2015
4YC3	25864384	CDK1-cyclinB1-CKS2 Apo	2015-02-19	2015
4YC6	25864384	CDK1/CKS1	2015-02-19	2015
5HQ0	25864384	Ternary complex of human proteins CDK1, cyclin B and CKS2, bound to an inhibitor	2016-01-21	2015
5LQF	28005359	CDK1-cyclin B1-CKS2 in complex with NU6102	2016-08-17	2017
CDK2				
1AQ1	9334743	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR STAUROSPORINE	1997-08-05	1997
1B38	10085115	HUMAN CDK2	1998-12-17	1999
1B39	10085115	HUMAN CDK2 PHOSPHORYLATED ON THR 160	1998-12-17	1999
1BUH	8601310	CRYSTAL STRUCTURE OF THE HUMAN CDK2 KINASE COMPLEX WITH CELL CYCLE-REGULATORY PROTEIN	1998-09-03	1996
1CKP	9677190	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR PURVALANOL B	1998-07-14	1998
1DI8	10633045	THE STRUCTURE OF CDK2 IN COMPLEX WITH 4-[3-HYDROXYANILINO]-6,7-DIMETHOXYQUINAZOLINE	1999-11-29	2000
1DM2	10662688	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR HYMENIALDISINE	1999-12-13	2000
1E1V	10956187	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR NU2058	2000-05-11	2000
1E1X	10956187	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR NU6027	2000-05-11	2000
1E9H	11377199	THR 160 PHOSPHORYLATED CDK2 - HUMAN CYCLIN A3 COMPLEX WITH THE INHIBITOR INDIRUBIN-5-	2000-10-16	2001
1F5Q	10856233	CRYSTAL STRUCTURE OF MURINE GAMMA HERPESVIRUS CYCLIN COMPLEXED TO HUMAN CDK2	2000-06-15	2000
1FIN	7630397	CYCLIN A-CDK2 COMPLEX	1996-07-14	1995
1FQ1	11463386	CRYSTAL STRUCTURE OF KINASE ASSOCIATED PHOSPHATASE (KAP) IN COMPLEX WITH PHOSPHO-CDK2	2000-09-01	2001
1FVT	11141566	THE STRUCTURE OF CDK2 IN COMPLEX WITH AN OXINDOLE INHIBITOR	2000-09-20	2001
1FVV	11141566	THE STRUCTURE OF CDK2-CYCLIN A IN COMPLEX WITH AN OXINDOLE INHIBITOR	2000-09-20	2001
1G5S	11170642	CRYSTAL STRUCTURE OF HUMAN CDK2 IN COMPLEX WITH THE INHIBITOR H717	2000-11-02	2001
1GIH	11335721	HUMAN CDK2 COMPLEXED WITH THE CDK4 INHIBITOR	2001-02-06	2001
1GII	11335721	HUMAN CDK2 COMPLEXED WITH THE CDK4 INHIBITOR	2001-02-06	2001
1GIJ	11335721	HUMAN CDK2 COMPLEXED WITH THE CDK4 INHIBITOR	2001-02-06	2002
1GY3	12044161	PCDK2-CYCLIN A IN COMPLEX WITH MGADP, NITRATE AND PEPTIDE SUBSTRATE	2002-04-19	2002
1GZ8	12139449	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR 2-Amino-6-(3'-methyl-2'-oxo)butoxypurine	2002-05-17	2002
1H00	12941311	CDK2 IN COMPLEX WITH A DISUBSTITUTED 4, 6-BIS ANILINO PYRIMIDINE CDK4 INHIBITOR	2002-06-10	2003
1H01	12941311	CDK2 IN COMPLEX WITH A DISUBSTITUTED 2, 4-BIS ANILINO PYRIMIDINE CDK4 INHIBITOR	2002-06-10	2003
1H07	12941311	CDK2 IN COMPLEX WITH A DISUBSTITUTED 4, 6-BIS ANILINO PYRIMIDINE CDK4 INHIBITOR	2002-06-11	2003
1H08	12941311	CDK2 IN COMPLEX WITH A DISUBSTITUTED 2, 4-BIS ANILINO PYRIMIDINE CDK4 INHIBITOR	2002-06-11	2003
1H0V	12139449	HUMAN CDK2 IN COMPLEX WITH THE INHIBITOR 2-AMINO-6-[(R)-PYRROLIDINO-5'-YL]METHOXYPURINE	2002-06-27	2002
1H0W	12139449	HUMAN CDK2 IN COMPLEX WITH THE INHIBITOR 2-AMINO-6-[CYCLOHEX-3-ENYL]METHOXYPURINE	2002-06-27	2002
1H1P	12244298	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-cyclin A COMPLEXED WITH THE INHIBITOR NU2058	2002-07-21	2002
1H1Q	12244298	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-cyclin A COMPLEXED WITH THE INHIBITOR NU6094	2002-07-21	2002
1H1R	12244298	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-cyclin A COMPLEXED WITH THE INHIBITOR NU6086	2002-07-21	2002
1H1S	12244298	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-cyclin A COMPLEXED WITH THE INHIBITOR NU6102	2002-07-21	2002
1H24	12501191	CDK2-cyclin A IN COMPLEX WITH A 9 RESIDUE RECRUITMENT PEPTIDE FROM E2F	2002-07-31	2002
1H25	12501191	CDK2-cyclin A IN COMPLEX WITH AN 11-RESIDUE RECRUITMENT PEPTIDE FROM RETINOBLASTOMA-	2002-07-31	2002
1H26	12501191	CDK2-cyclin A IN COMPLEX WITH AN 11-RESIDUE RECRUITMENT PEPTIDE FROM P53	2002-07-31	2002
1H27	12501191	CDK2-cyclin A IN COMPLEX WITH AN 11-RESIDUE RECRUITMENT PEPTIDE FROM P27	2002-07-31	2002
1H28	12501191	CDK2-cyclin A IN COMPLEX WITH AN 11-RESIDUE RECRUITMENT PEPTIDE FROM P107	2002-07-31	2002
1HCK	8917641	HUMAN CDK2	1996-06-03	1996
1HCL	8917641	HUMAN CDK2	1996-06-03	1996
1JST	8756328	PHOSPHORYLATED CYCLIN-DEPENDENT KINASE-2 BOUND TO CYCLIN A	1996-07-03	1996
1JSU	8684460	P27(KIP1)/CYCLIN A-CDK2 COMPLEX	1996-07-03	1996

1JSV	11604388	The structure of CDK2 in complex with 4-[(6-amino-4-pyrimidinyl)amino]benzenesulfonamide	2001-08-19	2001
1JVP	11755359	Crystal structure of human CDK2 (unphosphorylated) in complex with PKF049-365	2001-08-31	2002
1KE5	11728181	CDK2 complexed with N-methyl-4-{[(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]amino}benzenesulfonamide	2001-11-14	2001
1KE6	11728181	CDK2 COMPLEXED WITH N-METHYL-{4-[2-(7-OXO-6,7-DIHYDRO-8H-[1,3]THIAZOLO[5,4-E]INDOL-8-	2001-11-14	2001
1KE7	11728181	CDK2 COMPLEXED WITH 3-{[(2,2-DIOXIDO-1,3-DIHYDRO-2-BENZOTHIEN-5-YL)AMINO]METHYLENE}-5-(1,3-	2001-11-14	2001
1KE8	11728181	CDK2 COMPLEXED WITH 4-{[(2-OXO-1,2-DIHYDRO-3H-INDOL-3-YLIDENE)METHYL]AMINO}-N-(1,3-THIAZOL-2-	2001-11-14	2001
1KE9	11728181	CDK2 COMPLEXED WITH 3-{[4-({[AMINO(IMINO)METHYL]AMINOSULFONYL)ANILINO]METHYLENE}-2-OXO-2,3-	2001-11-14	2001
1OGU	12941338	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-cyclin A COMPLEXED WITH A 2-ARYLAMINO-4-	2003-05-13	2003
1OI9	15239650	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-cyclin A COMPLEXED WITH A 6-CYCLOHEXYLMETHYLOXY-2-	2003-06-10	2004
1OIQ	12941325	IMIDAZOPYRIDINES: A POTENT AND SELECTIVE CLASS OF CYCLIN-DEPENDENT KINASE INHIBITORS	2003-06-24	2003
1OIR	12941325	IMIDAZOPYRIDINES: A POTENT AND SELECTIVE CLASS OF CYCLIN-DEPENDENT KINASE INHIBITORS	2003-06-24	2003
1OIT	12941325	IMIDAZOPYRIDINES: A POTENT AND SELECTIVE CLASS OF CYCLIN-DEPENDENT KINASE INHIBITORS	2003-06-24	2003
1OIU	15239650	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-cyclin A COMPLEXED WITH A 6-CYCLOHEXYLMETHYLOXY-2-	2003-06-26	2004
1OIY	15239650	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-cyclin A COMPLEXED WITH A 6-CYCLOHEXYLMETHYLOXY-2-	2003-06-26	2004
1OKV	14656438	Cyclin A binding groove inhibitor H-Arg-Arg-Leu-Ile-Phe-NH2	2003-07-30	2003
1OKW	14656438	Cyclin A binding groove inhibitor Ac-Arg-Arg-Leu-Asn-(m-Cl-Phe)-NH2	2003-07-31	2003
1OL1	14656438	Cyclin A binding groove inhibitor H-Cit-Cit-Leu-Ile-(p-F-Phe)-NH2	2003-08-04	2003
1OL2	14656438	Cyclin A binding groove inhibitor H-Arg-Arg-Leu-Asn-(p-F-Phe)-NH2	2003-08-05	2003
1P2A	12852944	The structure of CDK2 with a trisubstituted naphthostyril inhibitor	2003-04-15	2003
1P5E	12869192	The structure of phospho-CDK2-cyclin A in complex with the inhibitor 4,5,6,7-tetrabromobenzotriazole (TBS)	2003-04-26	2003
1PF8	14550307	Crystal Structure of Human CDK2 Complexed with a Nucleoside Inhibitor	2003-05-24	2003
1PKD		THE CRYSTAL STRUCTURE OF UCN-01 IN COMPLEX WITH PHOSPHO-CDK2-cyclin A	2003-06-05	
1PW2	12679018	APO STRUCTURE OF HUMAN CDK2	2003-06-30	2003
1PXI	12679018	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR 4-(2,5-Dichloro-thiophen-3-yl)-pyrimidin-2-ylamine	2003-07-04	2003
1PXJ	12679018	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR 4-(2,4-Dimethyl-thiazol-5-yl)-pyrimidin-2-ylamine	2003-07-04	2003
1PXK	12679018	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR N-[4-(2,4-Dimethyl-thiazol-5-yl)pyrimidin-2-yl]-N'-	2003-07-04	2003
1PXL	12679018	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR [4-(2,4-Dimethyl-thiazol-5-yl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-amine	2003-07-04	2003
1PXM	15027857	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR 3-[4-(2,4-Dimethyl-thiazol-5-yl)-pyrimidin-2-ylamino]-phenol	2003-07-04	2004
1PXN	15027857	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR 4-[4-(4-Methyl-2-methylamino-thiazol-5-yl)-pyrimidin-2-ylamino]-	2003-07-04	2004
1PXO	15027857	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR [4-(2-Amino-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-	2003-07-04	2004
1PXP	15027857	HUMAN CDK2 COMPLEXED WITH THE INHIBITOR N-[4-(2,4-Dimethyl-thiazol-5-yl)-pyrimidin-2-yl]-N',N'-dimethyl-	2003-07-04	2004
1PYE	14749470	Crystal structure of CDK2 with inhibitor	2003-07-08	2004
1QMZ	10559988	PHOSPHORYLATED CDK2-CYCLIN A-SUBSTRATE PEPTIDE COMPLEX	1999-10-11	1999
1R78	15012993	CDK2 complex with a 4-alkynyl oxindole inhibitor	2003-10-20	2004
1URC	15455144	Cyclin A binding groove inhibitor Ace-Arg-Lys-Leu-Phe-Gly	2003-10-28	2004
1URW	15081018	CDK2 IN COMPLEX WITH AN IMIDAZO[1,2-B]PYRIDAZINE	2003-11-11	2004
1V1K	12941311	CDK2 IN COMPLEX WITH A DISUBSTITUTED 4, 6-BIS ANILINO PYRIMIDINE CDK4 INHIBITOR	2004-04-16	2003
1VYW	15189033	STRUCTURE OF CDK2-cyclin A WITH PNU-292137	2004-05-07	2004
1VYZ	15189033	STRUCTURE OF CDK2 COMPLEXED WITH PNU-181227	2004-05-07	2004
1W0X	7479711	Crystal structure of human CDK2 in complex with the inhibitor olomoucine.	2004-06-14	1995
1W8C	24304238	CO-CRYSTAL STRUCTURE OF 6-CYCLOHEXYLMETHOXY-8-ISOPROPYL-9H-PURIN-2- YLAMINE AND	2004-09-20	2014
1W98	15660127	THE STRUCTURAL BASIS OF CDK2 ACTIVATION BY CYCLIN E	2004-10-07	2005
1WCC	15658854	screening for fragment binding by X-ray crystallography	2004-11-12	2005
1Y8Y	15686876	Crystal structure of human CDK2 complexed with a pyrazolo[1,5-a]pyrimidine inhibitor	2004-12-14	2005
1Y91	15686876	Crystal structure of human CDK2 complexed with a pyrazolo[1,5-a]pyrimidine inhibitor	2004-12-14	2005
1YKR	15780638	Crystal structure of CDK2 with an aminoimidazo pyridine inhibitor	2005-01-18	2005
2A0C	16003486	Human CDK2 in complex with olomoucine II, a novel 2,6,9-trisubstituted purine cyclin-dependent kinase inhibitor	2005-06-16	2005
2B52	14698155	Human CDK2 complexed with DPH-042562	2005-09-27	2004
2B53	11354366	Human CDK2 complexed with DIN-234325	2005-09-27	2001
2B54	15537345	Human CDK2 complexed with DIN-232305	2005-09-27	2004
2B55	12431051	Human CDK2 (CDK2) complexed with indenopyraxole DIN-101312	2005-09-27	2002
2BHE	15742375	HUMAN CDK2 IN COMPLEX WITH THE INHIBITOR 5-BROMO-INDIRUBINE	2005-01-10	2005

2BHH	15742375	HUMAN CDK2 IN COMPLEX WITH THE INHIBITOR 4-HYDROXYPIPERINDINESULFONYL-INDIRUBINE	2005-01-11	2005
2BKZ	15713378	STRUCTURE OF CDK2-CYCLIN A WITH PHA-404611	2005-02-23	2005
2BPM	15828833	STRUCTURE OF CDK2-CYCLIN A WITH PHA-630529	2005-04-21	2005
2BTR	16260160	STRUCTURE OF CDK2 COMPLEXED WITH PNU-198873	2005-06-06	2006
2BTS	16260160	STRUCTURE OF CDK2 COMPLEXED WITH PNU-230032	2005-06-06	2006
2C4G	16290148	STRUCTURE OF CDK2-CYCLIN A WITH PHA-533514	2005-10-19	2006
2C5N	16492568	DIFFERENTIAL BINDING OF INHIBITORS TO ACTIVE AND INACTIVE CDK2 PROVIDES INSIGHTS FOR DRUG DESIGN	2005-10-30	2006
2C5O	16492568	DIFFERENTIAL BINDING OF INHIBITORS TO ACTIVE AND INACTIVE CDK2 PROVIDES INSIGHTS FOR DRUG	2005-10-30	2006
2C5V	16492568	Differential Binding Of Inhibitors To Active And Inactive CDK2 Provides Insights For Drug Design	2005-11-02	2006
2C5X	16492568	DIFFERENTIAL BINDING OF INHIBITORS TO ACTIVE AND INACTIVE CDK2 PROVIDES INSIGHTS FOR DRUG	2005-11-03	2006
2C5Y	16492568	DIFFERENTIAL BINDING OF INHIBITORS TO ACTIVE AND INACTIVE CDK2 PROVIDES INSIGHTS FOR DRUG DESIGN	2005-11-03	2006
2C68	16325401	Crystal structure of the human CDK2 complexed with the triazolopyrimidine inhibitor	2005-11-08	2006
2C69	16325401	CRYSTAL STRUCTURE OF THE HUMAN CDK2 COMPLEXED WITH THE TRIAZOLOPYRIMIDINE INHIBITOR	2005-11-08	2006
2C6I	16325401	Crystal structure of the human CDK2 complexed with the triazolopyrimidine inhibitor	2005-11-10	2006
2C6K	16325401	Crystal structure of the human CDK2 complexed with the triazolopyrimidine inhibitor	2005-11-10	2006
2C6L	16325401	Crystal structure of the human CDK2 complexed with the triazolopyrimidine inhibitor	2005-11-10	2006
2C6M	16325401	Crystal structure of the human CDK2 complexed with the triazolopyrimidine inhibitor	2005-11-10	2006
2C6O	16325401	CRYSTAL STRUCTURE OF THE HUMAN CDK2 COMPLEXED WITH THE TRIAZOLOPYRIMIDINE INHIBITOR	2005-11-10	2006
2C6T	16325401	CRYSTAL STRUCTURE OF THE HUMAN CDK2 COMPLEXED WITH THE TRIAZOLOPYRIMIDINE INHIBITOR	2005-11-11	2006
2CCH	16707497	THE CRYSTAL STRUCTURE OF CDK2 CYCLIN A IN COMPLEX WITH A SUBSTRATE PEPTIDE DERIVED FROM CDC MODIFIED WITH A GAMMA-LINKED ATP ANALOGUE	2006-01-16	2006
2CCI	16707497	CRYSTAL STRUCTURE OF PHOSPHO-CDK2 CYCLIN A IN COMPLEX WITH A PEPTIDE CONTAINING BOTH THE SUBSTRATE AND RECRUITMENT SITES OF CDC6	2006-01-16	2006
2CJM	17095507	Mechanism of CDK inhibition by active site phosphorylation: CDK2 Y15p T160p in complex with cyclin A structure	2006-04-05	2007
2CLX	17064068	4-ARYLAZO-3,5-DIAMINO-1H-PYRAZOLE CDK INHIBITORS: SAR STUDY, CRYSTAL STRUCTURE IN COMPLEX WITH CDK2, SELECTIVITY, AND CELLULAR EFFECTS	2006-05-02	2006
2DS1	16876403	Human CDK2 complexed with the CDK4 inhibitor	2006-06-17	2006
2DUV	17178224	Structure of CDK2 with a 3-hydroxychromones	2006-07-27	2007
2EXM	7479711	Human CDK2 in complex with isopentenyladenine	2005-11-08	1995
2FVD	17064073	CDK2 (CDK2) with diaminopyrimidine inhibitor	2006-01-30	2006
2G9X	16669651	Structure of Thr 160 phosphorylated CDK2-cyclin A in complex with the inhibitor NU6271	2006-03-07	2006
2I40	16997559	CDK2-cyclin A complexed with a thiophene carboxamide inhibitor	2006-08-21	2006
2IW6	16942020	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-CYCLIN A COMPLEXED WITH A BISANILINOPYRIMIDINE INHIBITOR	2006-06-26	2006
2IW8	16942020	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-CYCLIN A F82H-L83V-H84D MUTANT WITH AN O6-CYCLOHEXYLMETHYLGUANINE INHIBITOR	2006-06-27	2006
2IW9	16942020	STRUCTURE OF HUMAN THR160-PHOSPHO CDK2-CYCLIN A COMPLEXED WITH A BISANILINOPYRIMIDINE INHIBITOR	2006-06-27	2006
2J9M	17131463	CRYSTAL STRUCTURE OF CDK2 IN COMPLEX WITH MACROCYCLIC AMINOPYRIMIDINE	2006-11-13	2007
2JGZ	17495531	CRYSTAL STRUCTURE OF PHOSPHO-CDK2 IN COMPLEX WITH CYCLIN B	2007-02-17	2007
2R3F	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3G	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3H	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3I	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3J	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3K	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3L	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3M	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008

2R3N	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3O	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3P	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3Q	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R3R	17937404	Crystal Structure of CDK2 with inhibitor	2007-08-29	2008
2R64	18353638	Crystal structure of a 3-aminoindazole compound with CDK2	2007-09-05	2008
2UUE	17051658	REPLACE: A strategy for Iterative Design of Cyclin Binding Groove Inhibitors	2007-03-02	2006
2UZB	17570665	CRYSTAL STRUCTURE OF HUMAN CDK2 COMPLEXED WITH A THIAZOLIDINONE INHIBITOR	2007-04-27	2007
2UZD	17570665	CRYSTAL STRUCTURE OF HUMAN CDK2 COMPLEXED WITH A THIAZOLIDINONE INHIBITOR	2007-04-27	2007
2UZE	17570665	CRYSTAL STRUCTURE OF HUMAN CDK2 COMPLEXED WITH A THIAZOLIDINONE INHIBITOR	2007-04-27	2007
2UZL	17570665	CRYSTAL STRUCTURE OF HUMAN CDK2 COMPLEXED WITH A THIAZOLIDINONE INHIBITOR	2007-04-30	2007
2UZN	17570665	CRYSTAL STRUCTURE OF HUMAN CDK2 COMPLEXED WITH A THIAZOLIDINONE INHIBITOR	2007-04-30	2007
2UZO	17570665	CRYSTAL STRUCTURE OF HUMAN CDK2 COMPLEXED WITH A THIAZOLIDINONE INHIBITOR	2007-04-30	2007
2V0D	17570665	CRYSTAL STRUCTURE OF HUMAN CDK2 COMPLEXED WITH A THIAZOLIDINONE INHIBITOR	2007-05-14	2007
2V22	17051658	REPLACE: A STRATEGY FOR ITERATIVE DESIGN OF CYCLIN BINDING GROOVE INHIBITORS	2007-05-31	2006
2VTA	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-13	2008
2VTH	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN	2008-05-15	2008
2VTI	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTJ	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTL	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTM	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTN	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTO	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTP	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTQ	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTR	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008

2VTS	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VTT	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-15	2008
2VU3	18656911	IDENTIFICATION OF N-(4-PIPERIDINYL)-4-(2,6-DICHLOROBENZOYLAMINO)-1H-PYRAZOLE-3-CARBOXAMIDE (AT7519), A NOVEL CYCLIN DEPENDENT KINASE INHIBITOR USING FRAGMENT-BASED X-RAY CRYSTALLOGRAPHY AND STRUCTURE BASED DRUG DESIGN.	2008-05-20	2008
2VV9	18617397	CDK2 IN COMPLEX WITH AN IMIDAZOLE PIPERAZINE	2008-06-04	2008
2W05	18815031	STRUCTURE OF CDK2 IN COMPLEX WITH AN IMIDAZOLYL PYRIMIDINE, COMPOUND 5B	2008-08-08	2008
2W06	18815031	STRUCTURE OF CDK2 IN COMPLEX WITH AN IMIDAZOLYL PYRIMIDINE, COMPOUND 5C	2008-08-08	2008
2W17	18996007	CDK2 IN COMPLEX WITH THE IMIDAZOLE PYRIMIDINE AMIDE, COMPOUND (S)-8B	2008-10-15	2008
2W1H	19143567	Fragment-Based Discovery of the Pyrazol-4-yl urea (AT9283), a Multi- targeted Kinase Inhibitor with Potent Aurora Kinase Activity	2008-10-17	2009
2WEV	19472269	Truncation and Optimisation of Peptide Inhibitors of CDK2, cyclin A Through Structure Guided Design	2009-04-01	2009
2WFY	19472269	Truncation and Optimisation of Peptide Inhibitors of CDK2, cyclin A Through Structure Guided Design	2009-04-15	2009
2WHB	19472269	Truncation and Optimisation of Peptide Inhibitors of CDK2, cyclin A Through Structure Guided Design	2009-05-03	2009
2WIH	19603809	STRUCTURE OF CDK2-CYCLIN A WITH PHA-848125	2009-05-13	2009
2WIP	19603809	STRUCTURE OF CDK2-CYCLIN A COMPLEXED WITH 8-ANILINO-1-METHYL-4,5-DIHYDRO- 1H-PYRAZOLO[4,3-H] QUINAZOLINE-3-CARBOXYLIC ACID	2009-05-14	2009
2WMA		STRUCTURAL AND THERMODYNAMIC CONSEQUENCES OF CYCLIZATION OF PEPTIDE LIGANDS FOR THE RECRUITMENT SITE OF CYCLIN A	2009-06-30	
2WMB		STRUCTURAL AND THERMODYNAMIC CONSEQUENCES OF CYCLIZATION OF PEPTIDE LIGANDS FOR THE RECRUITMENT SITE OF CYCLIN A	2009-06-30	
2WPA	20153204	OPTIMISATION OF 6,6-DIMETHYL PYRROLO 3,4-C PYRAZOLES: IDENTIFICATION OF PHA-793887, A POTENT CDK INHIBITOR SUITABLE FOR INTRAVENOUS DOSING	2009-08-03	2010
2WXV	20141146	STRUCTURE OF CDK2-CYCLIN A WITH A PYRAZOLO(4,3-H) QUINAZOLINE-3-CARBOXAMIDE INHIBITOR	2009-11-10	2010
2X1N	20146435	Truncation and Optimisation of Peptide Inhibitors of CDK2, cyclin A Through Structure Guided Design	2009-12-31	2010
2XMY	21035734	Discovery and Characterisation of 2-Anilino-4-(thiazol-5-yl) pyrimidine Transcriptional CDK Inhibitors as Anticancer Agents	2010-07-29	2010
2XNB	21035734	Discovery and Characterisation of 2-Anilino-4-(thiazol-5-yl) pyrimidine Transcriptional CDK Inhibitors as Anticancer Agents	2010-08-01	2010
3BHT	17804748	Structure of phosphorylated Thr160 CDK2-cyclin A in complex with the inhibitor meriolin 3	2007-11-29	2007
3BHU	17804748	Structure of phosphorylated Thr160 CDK2-cyclin A in complex with the inhibitor meriolin 5	2007-11-29	2007
3BHV	17804748	Structure of phosphorylated Thr160 CDK2-cyclin A in complex with the inhibitor variolin B	2007-11-29	2007
3DDP	18574471	Structure of phosphorylated Thr160 CDK2-cyclin A in complex with the inhibitor CR8	2008-06-06	2008
3DDQ	18574471	Structure of phosphorylated Thr160 CDK2-cyclin A in complex with the inhibitor roscovitine	2008-06-06	2008
3DOG	18790752	Structure of Thr 160 phosphorylated CDK2-cyclin A in complex with the inhibitor N-&-N1	2008-07-04	2008
3EID	18835709	CDK2-cyclinA complexed with a pyrazolopyridazine inhibitor	2008-09-15	2008
3EJ1	18835709	CDK2-cyclinA complexed with a pyrazolopyridazine inhibitor	2008-09-17	2008
3EOC	18929484	CDK2-cyclinA complexed with a imidazo triazin-2-amine	2008-09-26	2008
3EZR	19097791	CDK2 with indazole inhibitor 17 bound at its active site	2008-10-23	2009
3EZV	19097791	CDK2 with indazole inhibitor 9 bound at its active site	2008-10-23	2009
3F5X	19097791	CDK2-cyclin complex with indazole inhibitor 9 bound at its active site	2008-11-04	2009
3FZ1	19616942	Crystal structure of a benzthiophene inhibitor bound to human Cyclin-dependent Kinase-2 (CDK-2)	2009-01-23	2009
3IG7	19700321	Novel CDK5 inhibitors - crystal structure of inhibitor EFP with CDK-2	2009-07-27	2009
3IGG	19700321	Novel CDK5 inhibitors - crystal structure of inhibitor EFQ with CDK-2	2009-07-27	2009
3LE6	20832307	The structure of CDK2 (CKD2) with a pyrazolobenzodiazepine inhibitor	2010-01-14	2010

3LFN	20167481	Crystal structure of CDK2 with SAR57, an aminoindazole type inhibitor	2010-01-18	2010
3LFQ	20167481	Crystal structure of CDK2 with SAR60, an aminoindazole type inhibitor	2010-01-18	2010
3LFS	20167481	Crystal structure of CDK2 with SAR37, an aminoindazole type inhibitor	2010-01-18	2010
3MY5	20851342	CDK2-cyclinA in complex with DRB	2010-05-09	2010
3NS9	21080703	Crystal structure of CDK2 in complex with inhibitor BS-194	2010-07-01	2010
3PJ8	21417417	Structure of CDK2 in complex with a Pyrazolo[4,3-d]pyrimidine Bioisostere of Roscovitine.	2010-11-09	2011
3PXF	21291269	CDK2 in complex with two molecules of 8-anilino-1-naphthalene sulfonate	2010-12-09	2011
3PXQ	21291269	CDK2 in complex with 3 molecules of 8-anilino-1-naphthalene sulfonate	2010-12-10	2011
3PXR	21291269	Apo CDK2 crystallized from Jeffamine	2010-12-10	2011
3PXY	21291269	CDK2 in complex with inhibitor JWS648	2010-12-10	2011
3PXZ	21291269	CDK2 ternary complex with JWS648 and ANS	2010-12-10	2011
3PY0	21291269	CDK2 in complex with inhibitor SU9516	2010-12-10	2011
3PY1	21291269	CDK2 ternary complex with SU9516 and ANS	2010-12-10	2011
3QHR	21565702	Structure of a pCDK2-cyclinA transition-state mimic	2011-01-26	2011
3QHW	21565702	Structure of a pCDK2-cyclinA transition-state mimic	2011-01-26	2011
3QL8		CDK2 in complex with inhibitor JWS-6-260	2011-02-02	
3QQF		CDK2 in complex with inhibitor L1	2011-02-15	
3QQG		CDK2 in complex with inhibitor L2-5	2011-02-15	
3QQH		CDK2 in complex with inhibitor L2-2	2011-02-15	
3QQJ		CDK2 in complex with inhibitor L2	2011-02-15	
3QQK	23600925	CDK2 in complex with inhibitor L4	2011-02-15	2013
3QQL		CDK2 in complex with inhibitor L3	2011-02-15	
3QRT		CDK2 in complex with inhibitor NSK-MC2-55	2011-02-18	
3QRU		CDK2 in complex with inhibitor NSK-MC1-12	2011-02-18	
3QTQ	23600925	CDK2 in complex with inhibitor RC-1-137	2011-02-23	2013
3QTR	23600925	CDK2 in complex with inhibitor RC-1-148	2011-02-23	2013
3QTS	23600925	CDK2 in complex with inhibitor RC-2-12	2011-02-23	2013
3QTU	23600925	CDK2 in complex with inhibitor RC-2-132	2011-02-23	2013
3QTW	23600925	CDK2 in complex with inhibitor RC-2-13	2011-02-23	2013
3QTX	23600925	CDK2 in complex with inhibitor RC-2-35	2011-02-23	2013
3QTZ	23600925	CDK2 in complex with inhibitor RC-2-36	2011-02-23	2013
3QU0	23600925	CDK2 in complex with inhibitor RC-2-38	2011-02-23	2013
3QWJ		CDK2 in complex with inhibitor KVR-1-142	2011-02-28	
3QWK		CDK2 in complex with inhibitor KVR-1-150	2011-02-28	
3QX2		CDK2 in complex with inhibitor KVR-1-190	2011-03-01	
3QX4		CDK2 in complex with inhibitor KVR-1-78	2011-03-01	
3QXO		CDK2 in complex with inhibitor KVR-1-84	2011-03-02	
3QXP	23600925	CDK2 in complex with inhibitor RC-3-89	2011-03-02	2013
3QZF		CDK2 in complex with inhibitor JWS-6-52	2011-03-06	
3QZG		CDK2 in complex with inhibitor JWS-6-76	2011-03-06	
3QZH		CDK2 in complex with inhibitor KVR-1-124	2011-03-06	
3QZI		CDK2 in complex with inhibitor KVR-1-126	2011-03-06	
3R1Q		CDK2 in complex with inhibitor KVR-1-102	2011-03-11	
3R1S		CDK2 in complex with inhibitor KVR-1-127	2011-03-11	
3R1Y		CDK2 in complex with inhibitor KVR-1-134	2011-03-11	
3R28		CDK2 in complex with inhibitor KVR-1-140	2011-03-14	
3R6X		CDK2 in complex with inhibitor KVR-1-158	2011-03-22	
3R71		CDK2 in complex with inhibitor KVR-1-162	2011-03-22	
3R73		CDK2 in complex with inhibitor KVR-1-164	2011-03-22	

3R7E		CDK2 in complex with inhibitor KVR-1-67	2011-03-22	
3R7I		CDK2 in complex with inhibitor KVR-1-74	2011-03-22	
3R7U		CDK2 in complex with inhibitor KVR-1-75	2011-03-23	
3R7V		CDK2 in complex with inhibitor KVR-1-9	2011-03-23	
3R7Y		CDK2 in complex with inhibitor KVR-2-88	2011-03-23	
3R83		CDK2 in complex with inhibitor KVR-2-92	2011-03-23	
3R8L		CDK2 in complex with inhibitor L3-4	2011-03-24	
3R8M		CDK2 in complex with inhibitor L3-3	2011-03-24	
3R8P		CDK2 in complex with inhibitor NSK-MC1-6	2011-03-24	
3R8U	23600925	CDK2 in complex with inhibitor RC-1-132	2011-03-24	2013
3R8V	23600925	CDK2 in complex with inhibitor RC-1-135	2011-03-24	2013
3R8Z	23600925	CDK2 in complex with inhibitor RC-1-136	2011-03-24	2013
3R9D	23600925	CDK2 in complex with inhibitor RC-2-135	2011-03-25	2013
3R9H	23600925	CDK2 in complex with inhibitor RC-2-142	2011-03-25	2013
3R9N	23600925	CDK2 in complex with inhibitor RC-2-21	2011-03-25	2013
3R9O	23600925	CDK2 in complex with inhibitor RC-2-143	2011-03-25	2013
3RAH	23600925	CDK2 in complex with inhibitor RC-2-22	2011-03-28	2013
3RAI		CDK2 in complex with inhibitor KVR-1-160	2011-03-28	
3RAK	23600925	CDK2 in complex with inhibitor RC-2-32	2011-03-28	2013
3RAL	23600925	CDK2 in complex with inhibitor RC-2-34	2011-03-28	2013
3RJC	23600925	CDK2 in complex with inhibitor L4-12	2011-04-15	2013
3RK5	23600925	CDK2 in complex with inhibitor RC-2-72	2011-04-17	2013
3RK7	23600925	CDK2 in complex with inhibitor RC-2-71	2011-04-17	2013
3RK9	23600925	CDK2 in complex with inhibitor RC-2-74	2011-04-17	2013
3RKB	23600925	CDK2 in complex with inhibitor RC-2-73	2011-04-17	2013
3RM6		CDK2 in complex with inhibitor KVR-2-80	2011-04-20	
3RM7		CDK2 in complex with inhibitor KVR-1-91	2011-04-20	
3RMF	23600925	CDK2 in complex with inhibitor RC-2-33	2011-04-20	2013
3RNI	23600925	CDK2 in complex with inhibitor RC-3-86	2011-04-22	2013
3ROY		CDK2 in complex with inhibitor KVR-1-154	2011-04-26	
3RPO		CDK2 in complex with inhibitor KVR-1-156	2011-04-27	
3RPR	23600925	CDK2 in complex with inhibitor RC-2-49	2011-04-27	2013
3RPV	23600925	CDK2 in complex with inhibitor RC-2-88	2011-04-27	2013
3RPY	23600925	CDK2 in complex with inhibitor RC-2-40	2011-04-27	2013
3RZB	23600925	CDK2 in complex with inhibitor RC-2-23	2011-05-11	2013
3S00	23600925	CDK2 in complex with inhibitor L4-14	2011-05-12	2013
3S0O	23600925	CDK2 in complex with inhibitor RC-1-138	2011-05-13	2013
3S1H	23600925	CDK2 in complex with inhibitor RC-2-39	2011-05-15	2013
3S2P	21684737	Crystal structure of CDK2 with a 2-aminopyrimidine compound	2011-05-17	2011
3SQQ	23600925	CDK2 in complex with inhibitor RC-3-96	2011-07-06	2013
3SW4		Crystal Structure of the CDK2 in complex with thiazolylpyrimidine inhibitor	2011-07-13	
3SW7		Crystal Structure of the CDK2 in complex with thiazolylpyrimidine inhibitor	2011-07-13	
3TI1	22893598	CDK2 in complex with SUNITINIB	2011-08-19	2012
3TIY	22893598	CDK2 in complex with NSC 35676	2011-08-22	2012
3TIZ	22893598	CDK2 in complex with NSC 111848	2011-08-22	2012
3TNW	22292676	Structure of CDK2-cyclin A in complex with CAN508	2011-09-02	2012
3ULI	22305584	Human CDK2 bound to azabenzimidazole derivative	2011-11-10	2012
3UNJ	22248356	CDK2 in complex with inhibitor YL1-038-31	2011-11-15	2012
3UNK	22248356	CDK2 in complex with inhibitor YL5-083	2011-11-15	2012

3WBL	24121337	Crystal structure of CDK2 in complex with pyrazolopyrimidine inhibitor	2013-05-20	2013
4ACM	22489897	CDK2 IN COMPLEX WITH 3-AMINO-6-(4-{[2-(DIMETHYLAMINO)ETHYL]SULFAMOYL}-PHENYL)-N-PYRIDIN-3-YLPYRAZINE-2-CARBOXAMIDE	2011-12-16	2012
4BCK	23252711	Structure of CDK2 in complex with cyclin A and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCM	23252711	Structure of CDK2 in complex with cyclin A and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCN	23252711	Structure of CDK2 in complex with cyclin A and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCO	23252711	Structure of CDK2 in complex with cyclin A and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCP	23301767	Structure of CDK2 in complex with cyclin A and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCQ	23252711	Structure of CDK2 in complex with cyclin A and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BGH	23671017	Crystal Structure of CDK2 in complex with pan-CDK Inhibitor	2013-03-26	2013
4BZD		Structure of CDK2 in complex with a benzimidazopyrimidine	2013-07-25	
4CFM	24304238	Structure-based design of C8-substituted O6-cyclohexylmethoxyguanine CDK1 and 2 inhibitors.	2013-11-18	2014
4CFN	24304238	Structure-based design of C8-substituted O6-cyclohexylmethoxyguanine CDK1 and 2 inhibitors.	2013-11-19	2014
4CFU	24304238	Structure-based design of C8-substituted O6-cyclohexylmethoxyguanine CDK1 and 2 inhibitors.	2013-11-19	2014
4CFV	24304238	Structure-based design of C8-substituted O6-cyclohexylmethoxyguanine CDK1 and 2 inhibitors.	2013-11-19	2014
4CFW	24304238	Structure-based design of C8-substituted O6-cyclohexylmethoxyguanine CDK1 and 2 inhibitors.	2013-11-19	2014
4CFX	24304238	Structure-based design of C8-substituted O6-cyclohexylmethoxyguanine CDK1 and 2 inhibitors.	2013-11-19	2014
4D1X	25768698	CDK2 in complex with Luciferin	2014-05-05	2015
4D1Z	25768698	CDK2 in complex with a Luciferin derivate	2014-05-05	2015
4EK3		Crystal structure of apo CDK2	2012-04-09	
4EK4		Crystal structure of the CDK2 in complex with aminopyrazole inhibitor	2012-04-09	
4EK5		Crystal structure of the CDK2 in complex with aminopyrazole inhibitor	2012-04-09	
4EK6		Crystal structure of the CDK2 in complex with aminopyrazole inhibitor	2012-04-09	
4EK8		Crystal structure of the CDK2 in complex with thiazolylpyrimidine inhibitor	2012-04-09	
4EOI	22921070	Thr 160 phosphorylated CDK2 K89D, Q131E - human cyclin A3 complex with the inhibitor RO3306	2012-04-14	2012
4EOJ	22921070	Thr 160 phosphorylated CDK2 H84S, Q85M, K89D - human cyclin A3 complex with ATP	2012-04-14	2012
4EOK	22921070	Thr 160 phosphorylated CDK2 H84S, Q85M, K89D - human cyclin A3 complex with the inhibitor NU6102	2012-04-14	2012
4EOL	22921070	Thr 160 phosphorylated CDK2 H84S, Q85M, K89D - human cyclin A3 complex with the inhibitor RO3306	2012-04-14	2012
4EOM	22921070	Thr 160 phosphorylated CDK2 H84S, Q85M, Q131E - human cyclin A3 complex with ATP	2012-04-14	2012
4EON	22921070	Thr 160 phosphorylated CDK2 H84S, Q85M, Q131E - human cyclin A3 complex with the inhibitor RO3306	2012-04-14	2012
4EOO	22921070	Thr 160 phosphorylated CDK2 Q131E - human cyclin A3 complex with ATP	2012-04-14	2012
4EOP	22921070	Thr 160 phosphorylated CDK2 Q131E - human cyclin A3 complex with the inhibitor RO3306	2012-04-14	2012
4EOQ	22921070	Thr 160 phosphorylated CDK2 WT - human cyclin A3 complex with ATP	2012-04-14	2012
4EOR	22921070	Thr 160 phosphorylated CDK2 WT - human cyclin A3 complex with the inhibitor NU6102	2012-04-14	2012
4EOS	22921070	Thr 160 phosphorylated CDK2 WT - human cyclin A3 complex with the inhibitor RO3306	2012-04-14	2012
4ERW	22893598	CDK2 in complex with staurosporine	2012-04-20	2012
4EZ3	22893598	CDK2 in complex with NSC 134199	2012-05-02	2012
4EZ7	22893598	CDK2 in complex with staurosporine and 2 molecules of 8-anilino-1-naphthalene sulfonic acid	2012-05-02	2012
4FKG		Crystal structure of the CDK2 in complex with aminopyrazole inhibitor	2012-06-13	
4FKI		Crystal Structure of the CDK2 in complex with aminopyrazole Inhibitor	2012-06-13	
4FKJ		Crystal structure of the CDK2 in complex with aminopyrazole inhibitor	2012-06-13	
4FKL		Crystal structure of the CDK2 in complex with thiazolylpyrimidine inhibitor	2012-06-13	
4FKO		Crystal structure of the CDK2 in complex with thiazolylpyrimidine inhibitor	2012-06-13	
4FKP		Crystal structure of the CDK2 in complex with oxindole inhibitor	2012-06-13	
4FKQ		Crystal structure of the CDK2 in complex with oxindole inhibitor	2012-06-13	
4FKR		Crystal structure of the CDK2 in complex with oxindole inhibitor	2012-06-13	
4FKS		Crystal structure of the CDK2 in complex with oxindole inhibitor	2012-06-13	
4FKT		Crystal structure of the CDK2 in complex with oxindole inhibitor	2012-06-13	
4FKU		Crystal structure of the CDK2 in complex with oxindole inhibitor	2012-06-13	

4FKV		Crystal structure of the CDK2 in complex with oxindole inhibitor	2012-06-13	
4FKW		Crystal structure of the CDK2 in complex with oxindole inhibitor	2012-06-13	
4FX3		Crystal Structure of the CDK2-cyclin A complex with oxindole inhibitor	2012-07-02	
4GCJ	23600925	CDK2 in complex with inhibitor RC-3-89	2012-07-30	2013
4I3Z	22891849	Structure of pCDK2-cyclinA bound to ADP and 2 Magnesium ions	2012-11-27	2012
4II5	22891849	Structure of pCDK2-cyclinA bound to ADP and 1 Magnesium ion	2012-12-19	2012
4KD1	24007471	CDK2 in complex with Dinaciclib	2013-04-24	2013
4LYN	12190313	Crystal structure of CDK2 (CDK2-wt) complex with (2s)-n-(5-(((5-tert-butyl-1,3-oxazol-2-yl)methyl)sulfanyl)-1,3-thiazol-2-yl)-2-phenylpropanamide	2013-07-31	2002
4NJ3	24332088	Modulating the interaction between CDK2 and cyclin A with a Quinoline-based inhibitor	2013-11-08	2014
4RJ3	25383627	CDK2 with EGFR inhibitor compound 8	2014-10-08	2014
5A14	26158339	Human CDK2 with type II inhibitor	2015-04-27	2015
5ANE	27050125	Crystal structure of CDK2 in complex with 6-methoxy-7H-purine processed with the CrystalDirect automated mounting and cryo-cooling technology	2015-09-07	2016
5ANG	27050125	Crystal structure of CDK2 in complex with 7-hydroxy-4-(morpholinomethyl)chromen-2-one processed with the CrystalDirect automated mounting and cryo-cooling technology	2015-09-07	2016
5ANI	27050125	Crystal structure of CDK2 in complex with 6-chloro-7H-purine processed with the CrystalDirect automated mounting and cryo-cooling technology	2015-09-07	2016
5ANJ	27050125	Crystal structure of CDK2 in complex with N-(9H-purin-6-yl)thiophene- 2-carboxamide processed with the CrystalDirect automated mounting and cryo-cooling technology	2015-09-07	2016
5ANK	27050125	Crystal structure of CDK2 in complex with 2,4,6-trioxo-1-phenyl- hexahydropyrimidine-5-carboxamide processed with the CrystalDirect automated mounting and cryo-cooling technology	2015-09-07	2016
5ANO	27050125	Crystal structure of CDK2 processed with the CrystalDirect automated mounting and cryo-cooling technology	2015-09-07	2016
5CYI	26320860	CDK2-cyclin A covalent complex with 6-(cyclohexylmethoxy)-N-(4-(vinylsulfonyl)phenyl)-9H-purin-2-amine (NU6300)	2015-07-30	2015
5D1J	15027863	CRYSTAL STRUCTURE OF CDK2 (CDK2-WT) COMPLEX WITH N-[5-[[[5-(1,1-DIMETHYLETHYL)-2-OXAZOLYL] METHYL]THIO]-2-THIAZOLYL]-4-PIPERIDINECARBOXAMIDE (BMS-387032)	2015-08-04	2004
5FP5	26655740	Structure of CDK2 with small-molecule ligand 4- fluorobenzoic acid (AT222) in an alternate binding site.	2015-11-27	2015
5FP6	26655740	Structure of CDK2 with small-molecule ligand 3-(4,7-dichloro-1H-indol-3-yl)prop-2-yn-1-ol (AT17833) in an alternate binding site.	2015-11-27	2015
5IEV	27090615	Crystal structure of BAY 1000394 (Roniciclib) bound to CDK2	2016-02-25	2016
5IEX	27090615	Crystal structure of (R,S)-S-{4-[(5-Bromo-4-{[(2R,3R)-2-hydroxy-1-methylpropyl]oxy}- pyrimidin-2-yl)amino]phenyl}-S-cyclopropylsulfoximide bound to CDK2	2016-02-25	2016
5IEY	27090615	Crystal structure of a CDK inhibitor bound to CDK2	2016-02-25	2016
5IF1	27090615	Crystal structure apo CDK2-cyclin A	2016-02-25	2016
5JQ5	28125165	Crystal structure of CDK2 in complex with inhibitor ICEC0942	2016-05-04	2017
5JQ8	28125165	Crystal structure of CDK2 in complex with inhibitor ICEC0943	2016-05-04	2017
5K4J	27227380	Crystal Structure of CDK2 in complex with compound 22	2016-05-20	2016
5L2W	27496135	The X-ray co-crystal structure of human CDK2-cyclin E and Dinaciclib.	2016-08-02	2016
5LMK	28039837	Structure of phopsho-CDK2-cyclin A in complex with an ATP-competitive inhibitor	2016-08-01	2016
5NEV	28005359	CDK2-cyclin A in complex with compound 73	2017-03-12	2017

CDK4				
2W96	19237565	Crystal structure of CDK4 in complex with a D-type cyclin	2009-01-21	2009
2W99	19237565	Crystal structure of CDK4 in complex with a D-type cyclin	2009-01-22	2009
2W9F	19237565	Crystal structure of CDK4 in complex with a D-type cyclin	2009-01-23	2009
2W9Z	19237565	Crystal structure of CDK4 in complex with a D-type cyclin	2009-01-30	2009
3G33	19237555	Crystal structure of CDK4/cyclin D3	2009-02-01	2009
5FWK	27339980	Atomic cryoEM structure of Hsp90-Cdc37-CDK4 complex	2016-02-17	2016
5FWL	27339980	Atomic cryoEM structure of Hsp90-Cdc37-CDK4 complex	2016-02-18	2016

5FWM	27339980	Atomic cryoEM structure of Hsp90-Cdc37-CDK4 complex	2016-02-18	2016
5FWP	27339980	Atomic cryoEM structure of Hsp90-Cdc37-CDK4 complex	2016-02-18	2016

CDK5

1H4L	11583627	Structure and regulation of the CDK5-p25(NCK5A) complex	2001-05-11	2001
1UNG	15689152	Structural mechanism for the inhibition of CDK5-p25 by roscovitine, aloisine and indirubin	2003-09-10	2005
1UNH	15689152	Structural mechanism for the inhibition of CDK5-p25 by roscovitine, aloisine and indirubin	2003-09-10	2005
1UNL	15689152	Structural mechanism for the inhibition of CDK5-p25 by roscovitine, aloisine and indirubin	2003-09-10	2005
3O0G	16039528	Crystal Structure of CDK5:p25 in complex with an ATP analogue	2010-07-19	2005
4AU8	22889803	Crystal structure of compound 4a in complex with CDK5, showing an unusual binding mode to the hinge region via a water molecule	2012-05-14	2012

CDK6

1BI7	9751050	Mechanism of G1 cyclin dependent kinase inhibition from the structure of the CDK6-p16INK4a tumor supressor complex	1998-06-22	1998
1BI8	9751050	Mechanism of G1 cyclin dependent kinase inhibition from the structure of the CDK6-p16INK4a tumor supressor complex	1998-06-22	1998
1BLX	9751051	p19INK4D/CDK6 complex	1998-07-21	1998
1G3N	11124804	Structure of a p18(INK4C)-CDK6-K-cyclin ternary complex	2000-10-24	2000
1JOW	11828325	Crystal structure of a complex of human CDK6 and a viral cyclin	2001-07-31	2002
1XO2	15689157	Crystal structure of a human CDK6 complex with a flavonol inhibitor, fisetin	2004-10-05	2005
2EUF	16789739	X-ray structure of human CDK6-Vcyclin in complex with the inhibitor PD0332991	2005-10-28	2006
2F2C	16789739	X-ray structure of human CDK6-Vcyclin with the inhibitor aminopurvalanol	2005-11-16	2006
3NUP	21038853	CDK6 (monomeric) in complex with inhibitor	2010-07-07	2010
3NUX	21038853	CDK6 (monomeric) in complex with inhibitor	2010-07-07	2010
4AUA	24900493	Liganded X-ray crystal structure of CDK6	2012-05-15	2012
4EZ5	24900493	CDK6 (monomeric) in complex with inhibitor	2012-05-02	2012
4TTH	24641103	Crystal structure of a CDK6-Vcyclin complex with inhibitor bound	2014-06-20	2014
5L2I	27496135	The X-ray co-crystal structure of human CDK6 and Palbociclib.	2016-08-01	2016
5L2S	27496135	The X-ray co-crystal structure of human CDK6 and Abemaciclib.	2016-08-02	2016
5L2T	27496135	The X-ray co-crystal structure of human CDK6 and Ribociclib.	2016-08-02	2016

CDK7

1UA2	15530371	Crystal structure of CDK7	2004-08-11	2004

CDK8

3RGF	21806996	Crystal Structure of human CDK8-cyclinC	2011-04-08	2011
4CRL	26416749	Crystal structure of human CDK8-cyclin C in complex with cortistatin A	2014-02-27	2015
4F6S	23630251	Crystal structure of human CDK8-cyclin C in complex with compound 7 (1-[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]urea)	2012-05-15	2013
4F6U	23630251	Crystal structure of human CDK8-cyclin C in complex with compound 5 (1-[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-3-[3-(morpholin-4-yl)propyl]urea)	2012-05-15	2013
4F6W	23630251	Crystal structure of human CDK8-cyclin C in complex with compound 1 (N-[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-4-[2-({[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]carbamoyl}amino)ethyl]piperazine-1-carboxamide)	2012-05-15	2013
4F70	23630251	Crystal structure of human CDK8-cyclin C in complex with compound 4 (1-[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-3-[2-(morpholin-4-yl)ethyl]urea)	2012-05-15	2013
4F7J	23630251	Crystal structure of human CDK8-cyclin C in complex with compound 3 (1-[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-3-(2-hydroxyethyl)urea)	2012-05-16	2013
4F7L	23630251	Crystal structure of human CDK8-cyclin C in complex with compound 2 (tert-butyl [3-({[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]carbamoyl}amino)propyl]carbamate)	2012-05-16	2013

4F7N	23630251	Crystal structure of human CDK8-cyclin C in complex with compound 11 (1-[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-3-(5-hydroxypentyl)urea)	2012-05-16	2013
4F7S	23630251	Crystal structure of human CDK8-cyclin C in the DMG-in conformation	2012-05-16	2013
4G6L	23630251	Crystal structure of human CDK8-cyclin C in the DMG-in conformation	2012-07-19	2013
5BNJ	26502155	CDK8-cyclin C in complex with 8-{3-Chloro-5-[4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-pyridin- 4-yl}-2,8-diaza-spiro[4.5]decan-1-one	2015-05-26	2015
5CEI	26985305	Crystal structure of CDK8-Cyclin C complex with compound 22	2015-07-06	2016
5FGK	26796641	CDK8-cyclin C in complex with 8-[3-(3-Amino-1H-indazol-6-yl)-5-chloro- pyridine-4-yl]-2,8-diaza-spiro[4.5]decan-1-one	2015-12-20	2016
5HBE	26796641	CDK8-cyclin C in complex with 8-[3-Chloro-5-(1-methyl-2,2-dioxo-2, 3-dihydro-1H-2l6-benzo[c]isothiazol-5-yl)-pyridin- 4-yl]-1-oxa-3,8-diaza-spiro[4.5]decan-2-one	2015-12-31	2016
5HBH	26796641	CDK8-cyclin C in complex with 5-{5-Chloro-4-[1-(2-methoxy-ethyl)-1,8-diaza-spiro[4.5]dec-8-yl]-pyridin-3-yl}-1-methyl-1,3-dihydro-benzo[c]isothiazole 2,2-dioxide	2015-12-31	2016
5HBJ	26796641	CDK8-cyclin C in complex with 8-[2-Amino-3-chloro-5-(1-methyl-1H-indazol-5-yl)-pyridin-4-yl]-2,8-diaza-spiro[4.5]decan-1-one	2015-12-31	2016
5HNB		CDK8-cyclin C in complex with [6-Hydroxy-3-(3-methyl-benzyl)-1H-indazol-5-yl]-((S)-3-hydroxy-pyrrolidin-1-yl)-methanone	2016-01-18	to be published
5HVY	27326333	CDK8-cyclin C in complex with compound 20	2016-01-28	2016
5I5Z	27326329	CDK8-cyclin C in complex with 8-(1-Methyl-2,2-dioxo-2,3-dihydro-1H-2l6-benzo[c]isothiazol-5-yl)-[1,6]naphthyridine-2-carboxylic acid methylamide	2016-02-15	2016
5ICP	27490956	CDK8-cyclin C in complex with [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-(5-methyl-imidazo[5,1-b][1,3,4]thiadiazol-2-yl)-methanone	2016-02-23	2016
5IDN	27490956	CDK8-cyclin C in complex with [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-methanone	2016-02-24	2016
5IDP	27490956	CDK8-cyclin C in complex with (3-Amino-1H-indazol-5-yl)-[(S)-2-(4-fluoro-phenyl)-piperidin-1-yl]-methanone	2016-02-24	2016

CDK9

3BLH	18566585	Crystal Structure of Human CDK9-cyclinT1	2007-12-11	2008
3BLQ	18566585	Crystal Structure of Human CDK9-cyclinT1 in Complex with ATP	2007-12-11	2008
3BLR	18566585	Crystal Structure of Human CDK9-cyclinT1 in complex with Flavopiridol	2007-12-11	2008
3LQ5	21779453	Structure of CDK9-CyclinT in complex with S-CR8	2010-02-08	2010
3MI9	20535204	Crystal structure of HIV-1 Tat complexed with human P-TEFb	2010-04-09	2010
3MIA	20535204	Crystal structure of HIV-1 Tat complexed with ATP-bound human P-TEFb	2010-04-09	2010
3MY1	20851342	Structure of CDK9-cyclinT1 in complex with DRB	2010-05-09	2010
3TN8	22292676	CDK9-cyclin T in complex with CAN508	2011-09-01	2012
3TNH	22292676	CDK9-cyclin T in complex with CAN508	2011-09-01	2012
3TNI	22292676	structure of CDK9-cyclin T F241L	2011-09-01	2012
4BCF	23252711	Structure of CDK9 in complex with cyclin T and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCG	23301767	Structure of CDK9 in complex with cyclin T and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCH	23252711	Structure of CDK9 in complex with cyclin T and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCI	23252711	Structure of CDK9 in complex with cyclin T and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4BCJ	23252711	Structure of CDK9 in complex with cyclin T and a 2-amino-4-heteroaryl- pyrimidine inhibitor	2012-10-02	2013
4EC8	22959624	Structure of full length CDK9 in complex with cyclinT and DRB	2012-03-26	2012
4EC9	22959624	Crystal structure of full-length CDK9 in complex with cyclin T	2012-03-26	2012
4IMY	23471103	The AFF4 scaffold binds human P-TEFb adjacent to HIV Tat	2013-01-03	2013
4OGR	24843025	Crystal structure of P-TEFb complex with AFF4 and Tat	2014-01-16	2014
4OR5	24727379	Crystal structure of HIV-1 Tat complexed with human P-TEFb and AFF4	2014-02-10	2014
5L1Z	27731797	TAR complex with HIV-1 Tat-AFF4-P-TEFb	2016-07-29	2016

CDK12

4CXA	26597175	Crystal structure of the human CDK12-cyclin K complex bound to AMPPNP	2014-04-04	2015
4NST	24662513	Crystal structure of human CDK12-cyclin K in complex with ADP-aluminum fluoride	2013-11-29	2014
4UN0	26597175	Crystal structure of the human CDK12-cyclin K complex	2014-05-22	2015
5ACB	27571479	Crystal Structure of the human CDK12-cyclin K Complex	2015-08-14	2016

CDK13

5EFQ	26748711	Crystal structure of human CDK13-Cyclin K in complex with ADP-aluminum fluoride	2015-10-24	2016

CDK16

3MTL		Crystal structure of the PCTAIRE1 kinase in complex with Indirubin E804	2010-04-30	to be published
5G6V		Crystal structure of the PCTAIRE1 kinase in complex with inhibitor	2016-08-16	to be published